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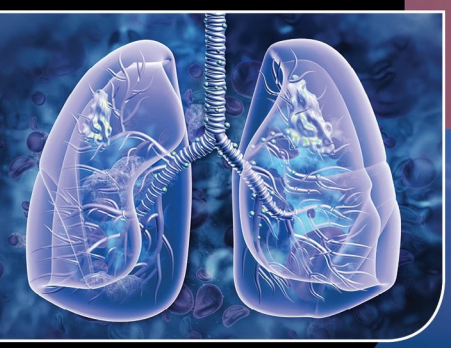

MAXINE A. PAPADAKIS

STEPHEN J. McPHEE

MICHAEL W. RABOW

ASSOCIATE EDITOR KENNETH R. McQUAID

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Edited by

Maxine A. Papadakis, MD
Professor of Medicine, Emeritus
Department of Medicine
University of California, San Francisco

Stephen J. McPhee, MD
Professor of Medicine, Emeritus
Division of General Internal Medicine
Department of Medicine
University of California, San Francisco

Michael W. Rabow, MD
Professor of Medicine and Urology
Division of Palliative Medicine
Department of Medicine
University of California, San Francisco

Associate Editor

Kenneth R. McQuaid, MD
Professor of Medicine
Department of Medicine
University of California, San Francisco

With Contributing Authors

New York Chicago San Francisco Athens London Madrid Mexico City
Milan New Delhi Singapore Sydney Toronto

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Contents

Authors

Christine Akamine, MD
Assistant Professor of Medicine, Section of Infectious Diseases, Department of Medicine, Baylor College of Medicine, Houston, Texas
akamine@bcm.edu
Viral & Rickettsial Infections

Michael J. Aminoff, MD, DSc, FRCP
Distinguished Professor and Endowed Chair in Parkinson's Disease Research, Department of Neurology, University of California, San Francisco; Attending Physician, University of California Medical Center, San Francisco
michael.aminoff@ucsf.edu
Nervous System Disorders

Charalambos Babis Andreadis, MD, MSCE
Professor of Clinical Medicine, Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco
Charalambos.Andreadis@ucsf.edu
Blood Disorders

Kevin L. Ard, MD, MPH
Faculty, Division of Infectious Diseases, Massachusetts General Hospital; Medical Director, National LGBTQIA+ Health Education Center, Fenway Institute; Assistant Professor of Medicine, Harvard Medical School, Boston, Massachusetts
kard@mgh.harvard.edu
Sexual & Gender Minority Health

Nayan Arora, MD
Assistant Professor, Division of Nephrology, Department of Medicine, University of Washington, Seattle, Washington
narora@uw.edu
Electrolyte & Acid-Base Disorders

David M. Barbour, PharmD, BCPS
Pharmacist, Denver, Colorado
dbarbour99@gmail.com
Drug References

Michael J. Blaha, MD, MPH
Professor of Medicine, Division of Cardiology, Department of Medicine; Director of Clinical Research, Ciccarone Center for the Prevention of Cardiovascular Disease; Johns Hopkins University School of Medicine, Baltimore, Maryland
mblaha1@jhmi.edu
Lipid Disorders

Bryn A. Boslett, MD
Associate Clinical Professor, Division of Infectious Diseases, Department of Medicine, University of California, San Francisco
Bryn.Boslett@ucsf.edu
Bacterial & Chlamydial Infections

Jill Brown, MD, MPH, MHS, FACOG
Medical Officer, Contraceptive Development Program, National Institute of Child Health and Human Development, Bethesda, Maryland
Jilleb75@yahoo.com
Gynecologic Disorders

Rachel Bystritsky, MD
Assistant Professor, Division of Infectious Diseases, Department of Medicine, University of California, San Francisco
Rachel.Bystritsky@ucsf.edu
Bacterial & Chlamydial Infections

Hugo Q. Cheng, MD
Clinical Professor of Medicine, Division of Hospital Medicine, Department of Medicine, University of California, San Francisco
quinny.cheng@ucsf.edu
Preoperative Evaluation & Perioperative Management

Peter V. Chin-Hong, MD
Professor of Medicine, Division of Infectious Diseases, Department of Medicine, University of California, San Francisco
peter.chin-hong@ucsf.edu
Common Problems in Infectious Diseases & Antimicrobial Therapy

Eva Clark, MD, PhD
Assistant Professor, Department of Medicine (Section of Infectious Diseases) and Department of Pediatrics (Section of Tropical Medicine), Baylor College of Medicine, Houston, Texas
eva.clark@bcm.edu
Viral & Rickettsial Infections

Russ Cucina, MD, MS
Professor of Hospital Medicine, Department of Medicine; Vice President, Genetic and Genomic Services and Chief Health Information Officer, UCSF Health System; University of California, San Francisco
russ.cucina@ucsf.edu
CMDT Online—Information Technology in Patient Care

Rand Dadasovich, MD, MS
Clinical Education Fellow, Division of Infectious Diseases, University of California, San Francisco
References

Marc A. Dall'Era, MD
Professor of Urology, Department of Urology, UC Davis Health, University of California, Davis
mdallera@ucdavis.edu
Genitourinary Cancers (in Chapter 39)

Lloyd E. Damon, MD
Professor of Clinical Medicine, Division of Hematology/Oncology, Department of Medicine; Director of Quality for the Adult Hematologic Malignancies and Blood and Marrow Transplantation Program, University of California, San Francisco
lloyd.damon@ucsf.edu
Blood Disorders

Tiffany O. Dea, PharmD, BCOP
Oncology Pharmacist, Veterans Affairs Health Care System, San Francisco, California; Adjunct Professor, Thomas J. Long School of Pharmacy and Health Sciences, Stockton, California
tiffany.dea@va.gov
Cancer

Charles DeBattista, DMH, MD
Professor of Psychiatry and Behavioral Sciences, Department of Psychiatry and Behavioral Sciences; Director, Depression Clinic and Research Program; Director of Medical Student Education in Psychiatry, Stanford University School of Medicine, Stanford, California
debattista@stanford.edu
Psychiatric Disorders

Madeline B. Deutsch, MD, MPH
Associate Professor of Clinical Family & Community Medicine, Department of Family & Community Medicine; Medical Director, UCSF Gender Affirming Health Program, University of California, San Francisco
Madeline.Deutsch@ucsf.edu
Sexual & Gender Minority Health

Chukwuka A. Didigu, MD, PhD
Clinical Fellow, Division of Hematology & Medical Oncology, Department of Medicine, University of California, San Francisco
References

Monara Dini, DPM
Associate Clinical Professor of Orthopedics, Department of Orthopedic Surgery, University of California, San Francisco
monara.dini@ucsf.edu
CMDT Online—Podiatric Disorders

Tonja C. Dirkx, MD
Chief, Nephrology Section, Veterans Affairs Portland Health Care System; Associate Professor of Medicine, Division of Nephrology, Department of Medicine, Oregon Health & Science University, Portland, Oregon
dirkxt@ohsu.edu
Kidney Disease

Brigid M. Dolan, MD, MEd
Associate Professor of Medicine and Medical Education, Division of General Internal Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine
brigid.dolan@northwestern.edu
CMDT Online—Women's Health Issues

Vanja C. Douglas, MD
Sara & Evan Williams Foundation Endowed Neurohospitalist Chair, Professor of Clinical Neurology, Department of Neurology, University of California, San Francisco
Vanja.Douglas@ucsf.edu
Nervous System Disorders

Jacque L. Duncan, MD
Professor of Clinical Ophthalmology, Department of Ophthalmology, University of California, San Francisco
jacque.duncan@ucsf.edu
Disorders of the Eyes & Lids

Neela Easwar, MD
Resident Physician, Department of Medicine, Weill Cornell Medicine, New York, New York
References

Sarah Adler Fink, RD, CDN, CNSC
Senior Clinical Dietitian, Department of Food and Nutrition, New York-Presbyterian Hospital/Weill Cornell Medical Center, New York, New York
Saa9108@nyp.org
Nutritional Support (in Chapter 29)

Paul A. Fitzgerald, MD
Clinical Professor of Medicine, Division of Endocrinology, Department of Medicine, University of California, San Francisco
paul.fitzgerald@ucsf.edu
Endocrine Disorders

Meghan E. Fitzpatrick, MD
Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
fitzpatrickme2@upmc.edu
Pulmonary Disorders

Lindy P. Fox, MD
Professor of Dermatology, Department of Dermatology, University of California, San Francisco
Lindy.Fox@ucsf.edu
Dermatologic Disorders; Callosities & Corns of Feet or Toes (CMDT Online—Podiatric Disorders)

Lawrence S. Friedman, MD
Professor of Medicine, Harvard Medical School; Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts; The Anton R. Fried, MD, Chair, Department of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts; Assistant Chief of Medicine, Massachusetts General Hospital, Boston
lfriedman@partners.org
Liver, Biliary Tract, & Pancreas Disorders; Hepatobiliary Cancers (in Chapter 39)

Monica Fung, MD, MPH
Assistant Professor, Division of Infectious Diseases, Department of Medicine, University of California, San Francisco
Monica.Fung@ucsf.edu
Common Problems in Infectious Diseases & Antimicrobial Therapy

Monica Gandhi, MD, MPH
Professor, Division of HIV, ID, and Global Medicine, Zuckerberg San Francisco General Hospital; University of California, San Francisco
Monica.Gandhi@ucsf.edu
HIV Infection & AIDS

Warren J. Gasper, MD
Associate Professor of Clinical Surgery, Division of Vascular and Endovascular Surgery, Department of Surgery, University of California, San Francisco
warren.gasper@ucsf.edu
Blood Vessel & Lymphatic Disorders

Armando E. Giuliano, MD, FACS, FRCSEd
Professor of Surgery, Linda and Jim Lippman Chair in Surgical Oncology; Director, Surgical Oncology; Associate Director, Cedars-Sinai Cancer Center, Los Angeles, California
armando.giuliano@cshs.org
Breast Disorders

Ralph Gonzales, MD, MSPH
Professor of Medicine, Division of General Internal Medicine, Department of Medicine; Associate Dean, Clinical Innovation and Chief Innovation Officer, UCSF Health; University of California, San Francisco
ralph.gonzales@ucsf.edu
Common Symptoms

Matthew Gorgone, DO, FACP
Pulmonary and Critical Care Fellow, Department of Medicine, University of Pittsburgh Medical Center
References

Christopher B. Granger, MD
Professor of Medicine, Division of Cardiology, Department of Medicine; Director, Cardiac Care Unit, Duke University Medical Center, Duke Clinical Research Institute, Durham, North Carolina
christopher.granger@dm.duke.edu
Heart Disease

Katherine Gruenberg, PharmD
Assistant Professor, School of Pharmacy, University of California, San Francisco
Katherine.Gruenberg@ucsf.edu
Common Problems in Infectious Diseases & Antimicrobial Therapy; CMDT Online—Anti-Infective Chemotherapeutic & Antibiotic Agents

B. Joseph Guglielmo, PharmD
Professor and Dean Emeritus, School of Pharmacy, University of California, San Francisco
BJoseph.Guglielmo@ucsf.edu
Common Problems in Infectious Diseases & Antimicrobial Therapy; CMDT Online—Anti-Infective Chemotherapeutic & Antibiotic Agents

Richard J. Hamill, MD
Professor of Medicine, Division of Infectious Diseases, Departments of Medicine and Molecular Virology & Microbiology, Baylor College of Medicine, Houston, Texas; Staff Physician, Infectious Diseases Section, Michael E. DeBakey Veterans Affairs Medical Center
rhamill@bcm.edu
Mycotic Infections

G. Michael Harper, MD
Professor, Division of Geriatrics, Department of Medicine, University of California, San Francisco School of Medicine; San Francisco Veterans Affairs Health Care System, San Francisco, California
Michael.Harper@ucsf.edu
Geriatric Disorders

Mitzi Hawkins, MD, MAS
Assistant Professor, Obstetrics, Gynecology & Reproductive Sciences, University of California, San Francisco; Chief, Division of Gynecology, San Francisco Veteran Affairs Health System
Mitzi.Hawkins@ucsf.edu
Sexual & Gender Minority Health

Sara A. Hurvitz, MD, FACP
Professor of Medicine; Division of Hematology/Oncology, Department of Internal Medicine; Director, Breast Oncology Program, University of California, Los Angeles
shurvitz@mednet.ucla.edu
Breast Disorders

James C. Iannuzzi, MD, MPH
Assistant Professor of Surgery, Division of Vascular and Endovascular Surgery, Department of Surgery, University of California, San Francisco
james.iannuzzi@ucsf.edu
Blood Vessel & Lymphatic Disorders

Leon I. Igel, MD, FACP, FTOS
Assistant Professor of Clinical Medicine, Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Weill Cornell Medical College, New York, New York
lei9004@med.cornell.edu
Nutritional Disorders & Obesity

Kevin P. Jackson, MD
Associate Professor of Medicine, Division of Cardiology, Department of Medicine; Director of Electrophysiology, Duke Raleigh Hospital, Duke University Medical Center, Durham, North Carolina
k.j@duke.edu
Heart Disease

J. Ashley Jefferson, MD, FRCP
Professor of Medicine, Division of Nephrology, Department of Medicine; Section Head, Nephrology, University of Washington Medical Center, Seattle, Washington
jashleyj@uw.edu
Electrolyte & Acid-Base Disorders

Jane Jih, MD, MPH, MAS
Associate Professor of Medicine, Division of General Internal Medicine, Department of Medicine, University of California, San Francisco
References

Meshell D. Johnson, MD
Professor of Medicine, Chief, Division of Pulmonary, Critical Care, and Sleep Medicine, San Francisco Veterans Affairs Health Care System; Associate Chair for Diversity, Equity, and Inclusion, Department of Medicine, University of California, San Francisco
meshell.johnson@ucsf.edu
Blood Vessel & Lymphatic Disorders; Alcohol Use Disorder (Alcoholism) (in Chapter 25)

Brian J. Jordan, MD
Assistant Professor, Department of Urology, University of Washington, Seattle
bjordan2@uw.edu
Urologic Disorders

Marianne A. Juarez, MD
Associate Clinical Professor, Department of Emergency Medicine, University of California, San Francisco
Marianne.Juarez@ucsf.edu
Disorders Related to Environmental Emergencies

Sakeen Kashem, MD, PhD
Resident, Department of Dermatology, University of California, San Francisco
References

Mitchell H. Katz, MD
President and Chief Executive Officer of NYC Health + Hospitals, New York, New York
mitchell.katz@nychhc.org
HIV Infection & AIDS

Todd Kiefer, MD
Associate Professor of Medicine, Division of Cardiology, Duke University Medical Center, Durham, North Carolina
todd.kiefer@duke.edu
Heart Disease

Whitney Kleinmann, MD
Maternal Fetal Medicine Fellow, Department of Obstetrics & Gynecology, UT Southwestern, Dallas, Texas
References

Elliott D. Kozin, MD
Assistant Professor of Otolaryngology - Head and Neck Surgery, Harvard Medical School, Boston, Massachusetts; Physician and Surgeon, Massachusetts Eye and Ear, Boston, Massachusetts
Elliott_Kozin@meei.harvard.edu
Otolaryngology Disorders

Mildred Kwan, MD, PhD
Assistant Professor of Medicine, Division of Rheumatology, Allergy & Immunology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina
mildred_kwan@med.unc.edu
Allergic & Immunologic Disorders (in Chapter 20)

Rossana Lau-Ng, MD
Assistant Professor, Section of Geriatrics, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts
rossana.lau-ng@bmc.org
Geriatric Disorders

Andrew D. Leavitt, MD
Professor, Departments of Medicine (Hematology) and Laboratory Medicine; Medical Director, UCSF Adult Hemophilia Treatment Center, University of California, San Francisco
andrew.leavitt@ucsf.edu
Disorders of Hemostasis, Thrombosis, & Antithrombotic Therapy

Chuanyi Mark Lu, MD
Professor and Vice Chair, Department of Laboratory Medicine, University of California, San Francisco; Chief, Lab Medicine Service, Veterans Affairs Health Care System, San Francisco, California
chuanyi.lu@ucsf.edu
Selected Pharmacogenetic Tests: Clinical Relevance (in Chapter 40); CMDT Online—Diagnostic Testing & Medical Decision Making; CMDT Online—Appendix: Therapeutic Drug Monitoring, Laboratory Reference Intervals, & Commonly Used Blood Specimen Collection Tubes

Anthony Luke, MD, MPH
Benioff Distinguished Professor in Sports Medicine, Department of Orthopaedics; Director, UCSF Primary Care Sports Medicine; Director, Human Performance Center at the Orthopaedic Institute, University of California, San Francisco
anthony.luke@ucsf.edu
Orthopedic Disorders & Sports Medicine

Lawrence R. Lustig, MD
Howard W. Smith Professor and Chair, Department of Otolaryngology—Head & Neck Surgery, Columbia University Irving Medical Center & New York Presbyterian Hospital, New York, New York
lrl2125@cumc.columbia.edu
Otolaryngology Disorders

C. Benjamin Ma, MD
Professor and Vice Chairman of Adult Clinical Operations, Department of Orthopaedic Surgery, University of California, San Francisco
MaBen@orthosurg.ucsf.edu
Orthopedic Disorders & Sports Medicine

Rebecca L. Manno, MD, MHS
Adjunct Assistant Professor, Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, Maryland
rmanno3@jhmi.edu
Rheumatologic, Immunologic, & Allergic Disorders

Umesh Masharani, MB, BS, MRCP (UK)
Professor of Medicine, Division of Endocrinology and Metabolism, Department of Medicine, University of California, San Francisco
umesh.masharani@ucsf.edu
Diabetes Mellitus & Hypoglycemia

Kenneth H. Mayer, MD
Professor of Medicine, Harvard Medical School; Co-Chair and Medical Research Director, The Fenway Institute; Director of HIV Prevention Research, Beth Israel Deaconess Medical Center, Boston, Massachusetts
kmayer@fenwayhealth.org
Sexual & Gender Minority Health

Kenneth R. McQuaid, MD
Professor of Medicine, Marvin H. Sleisenger Endowed Chair and Vice-Chairman, Department of Medicine, University of California, San Francisco; Chief, Medical Service, San Francisco Veterans Affairs Medical Center
Kenneth.McQuaid@ucsf.edu
Gastrointestinal Disorders; Alimentary Tract Cancers (in Chapter 39)

Darshan Mehta, MD, MPH
Assistant Professor of Medicine, Harvard Medical School; Medical Director, Benson-Henry Institute for Mind-Body Medicine, Massachusetts General Hospital; Director, Office for Well-Being, Center for Faculty Development, Massachusetts General Hospital; Director of Education, Osher Center for Integrative Medicine, Harvard Medical School and Brigham and Women's Hospital; Boston, Massachusetts
dmehta@partners.org
CMDT Online—Integrative Medicine

Raj Mitra, MD
Senator Robert J. Dole Professor and Chair, Department of Rehabilitation Medicine, University of Kansas Medical Center, Kansas City, Kansas
rmitra@kumc.edu
Opioids (in Chapter 5, Palliative Care & Pain Management)

Paul L. Nadler, MD
Clinical Professor of Medicine; Division of General Internal Medicine, Department of Medicine; Director, UCSF Adult Urgent Care; University of California, San Francisco
Paul.Nadler@ucsf.edu
Common Symptoms

Anand Narayanan, MD
Clinical Fellow, Endocrinology, Department of Medicine, University of California, San Francisco
References

Jacqueline A. Nemer, MD, FACEP
Professor of Emergency Medicine; Department of Emergency Medicine; Director of Value; Medical Director, Clinical Documentation Integrity, Department of Quality, University of California, San Francisco
jacqueline.nemer@ucsf.edu
Disorders Related to Environmental Emergencies

Akinyemi Oni-Orisan, PharmD, PhD
Assistant Professor, Department of Clinical Pharmacy University of California, San Francisco
akinyemi.oni-orisan@ucsf.edu
Unconscious Bias Reviewer

Steven Z. Pantilat, MD
Professor of Medicine, Department of Medicine;
Kates-Burnard and Hellman Distinguished Professor of Palliative Care; Chief, Division of Palliative Medicine, University of California, San Francisco
steve.pantilat@ucsf.edu
Palliative Care & Pain Management

Neeti B. Parikh, MD
Assistant Professor of Ophthalmology, Department of Ophthalmology, University of California, San Francisco
Neeti.Parikh@ucsf.edu
Disorders of the Eyes & Lids

Charles B. Parks, DPM
Associate Clinical Professor, Chief of Podiatric Surgery Division, Department of Orthopedic Surgery, University of California, San Francisco
Charles.Parks@ucsf.edu
CMDT Online—Podiatric Disorders

Susan S. Philip, MD, MPH
Assistant Clinical Professor, Division of Infectious Diseases, Department of Medicine, University of California, San Francisco; Disease Prevention and Control Branch, Population Health Division, San Francisco Department of Public Health, San Francisco, California
susan.philip@sfdph.org
Spirochetal Infections

Michael Pignone, MD, MPH
Professor of Medicine; Chair, Department of Medicine, Dell Medical School, The University of Texas at Austin
pignone@austin.utexas.edu
Disease Prevention & Health Promotion

Lawrence Poree, MD, MPH, PhD
Professor of Anesthesia and Pain Medicine, Department of Anesthesia & Perioperative Care, University of California, San Francisco
Lawrence.Poree@ucsf.edu
Palliative Care & Pain Management

Niall T. Prendergast, MD
Fellow, Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
niall.prendergast@gmail.com
Pulmonary Disorders

Erika Leemann Price, MD, MPH
Clinical Professor, Department of Medicine, University of California, San Francisco Hospitalist, San Francisco Veterans Affairs Health Care System
erika.price@ucsf.edu
Disorders of Hemostasis, Thrombosis, & Antithrombotic Therapy

Reed E. Pyeritz, MD, PhD
William Smilow Professor of Medicine and Genetics, Emeritus, Raymond and Ruth Perelman School of Medicine of the University of Pennsylvania, Philadelphia
reed.pyeritz@pennmedicine.upenn.edu
Genetic & Genomic Disorders

Michael W. Rabow, MD
Professor of Clinical Medicine and Urology, Division of Palliative Medicine, Department of Medicine; Helen Diller Family Chair in Palliative Care; Director, Symptom Management Service, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco
Mike.Rabow@ucsf.edu
Palliative Care & Pain Management

Kristin S. Raj, MD
Clinical Associate Professor of Psychiatry, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California
kraj@stanford.edu
Psychiatric Disorders

Belinda Rivera-Lebron, MD, MS, FCCP
Associate Professor of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
riveralebronbn@upmc.edu
Pulmonary Disorders

Scott W. Roberts, MD
Professor of Obstetrics and Gynecology, Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, Texas
scott.roberts@utsouthwestern.edu
Obstetrics & Obstetric Disorders

Patricia A. Robertson, MD
Professor of Obstetrics and Gynecology, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco
Patricia.Robertson@ucsf.edu
Sexual & Gender Minority Health

Vanessa L. Rogers, MD
Professor of Obstetrics and Gynecology, Department of Obstetrics and Gynecology; Chief, Division of Education and Faculty Development, University of Texas Southwestern Medical Center, Dallas, Texas
vanessa.rogers@utsouthwestern.edu
Obstetrics & Obstetric Disorders

Stacey R. Rose, MD, FACP, FIDSA
Assistant Professor of Internal Medicine, Division of Infectious Diseases, Department of Medicine; Associate Dean of Curriculum, Baylor College of Medicine, Houston, Texas
srrose@bcm.edu
Mycotic Infections

Nicole Rosendale, MD
Assistant Professor of Neurology, Neurohospitalist Division, Department of Neurology, University of California, San Francisco
nicole.rosendale@ucsf.edu
Sexual & Gender Minority Health

Philip J. Rosenthal, MD
Professor of Medicine, Department of Medicine, University of California, San Francisco; Associate Chief, Division of HIV, Infectious Diseases, and Global Medicine, Zuckerberg San Francisco General Hospital
philip.rosenthal@ucsf.edu
Protozoal & Helminthic Infections

René Salazar, MD
Professor of Internal Medicine and Medical Education, Department of Medicine, Dell Medical School, The University of Texas at Austin
rene.salazar@austin.utexas.edu
Disease Prevention & Health Promotion

Katherine Sanders, MD
Research Resident, Department of Surgery, University of California, San Francisco
References

Katherine H. Saunders, MD
Assistant Professor of Clinical Medicine, Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Weill Cornell Medicine, New York, New York
kph2001@med.cornell.edu
Nutritional Disorders & Obesity

Gerami D. Seitzman, MD
Associate Professor of Ophthalmology, Department of Ophthalmology, Francis I. Proctor Foundation, University of California, San Francisco
gerami.seitzman@ucsf.edu
Disorders of the Eyes & Lids

Ann Cai Shah, MD
Assistant Clinical Professor of Anesthesia and Pain Medicine, Department of Anesthesia and Perioperative Care, University of California, San Francisco
ann.shah@ucsf.edu
Palliative Care & Pain Management

Wayne X. Shandera, MD
Associate Professor of Medicine, Department of Medicine, Baylor College of Medicine, Houston, Texas
shandera@bcm.tmc.edu
Viral & Rickettsial Infections

Kanade Shinkai, MD, PhD
Professor of Dermatology, Department of Dermatology, University of California, San Francisco
Kanade.Shinkai@ucsf.edu
Dermatologic Disorders; Callosities & Corns of Feet or Toes (CMDT Online—Podiatric Disorders)

Katerina Shvartsman, MD, FACOG
Associate Professor of Obstetrics and Gynecology, Department of Obstetrics and Gynecology, Uniformed Services University, Bethesda, Maryland
Gynecologic Disorders

Craig Smollin, MD
Professor of Emergency Medicine, Department of Emergency Medicine, University of California, San Francisco; Medical Director, California Poison Control System—San Francisco Division
Craig.Smollin@ucsf.edu
Poisoning

Mathew Sorensen, MD, MS, FACS
Associate Professor of Urology, Department of Urology, University of Washington, Seattle; Residency Program Director, Department of Urology; Director, Comprehensive Metabolic Stone Clinic, Puget Sound Veterans Affairs Health Care System
mathews@uw.edu
Urologic Disorders

Matthew A. Spinelli, MD, MAS
Assistant Professor, Division of HIV, ID, and Global Medicine, Zuckerberg San Francisco General Hospital; University of California, San Francisco
Matthew.Spinelli@ucsf.edu
HIV Infection & AIDS

Gaelen Stanford-Moore, MD, MPhil
Resident Physician, Otolaryngology/Head and Neck Surgery University of California, San Francisco
References

Michael Sutters, MD, MRCP (UK)
Attending Nephrologist, Virginia Mason Medical Center, Seattle, Washington
michael.sutters@commonspirit.org
Systemic Hypertension

Teresa K. Tarrant, MD
Associate Professor, Department of Medicine, Division of Rheumatology and Immunology, Duke University Health System, Durham, North Carolina
teresa.tarrant@duke.edu
Allergic & Immunologic Disorders (in Chapter 20)

Philip Tiso, MFA
Principal Editor, Division of General Internal Medicine, University of California, San Francisco
References

Carling Ursem, MD
Assistant Professor, Division of Hematology and Oncology, Department of Medicine, University of California, San Francisco; Staff Physician, Veterans Affairs Health Care System, San Francisco
Carling.Ursem@ucsf.edu
Alimentary Tract Cancers (in Chapter 39)

Jonathan A. Waitman, MD
Assistant Professor of Medicine, Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Weill Cornell Medicine, New York, New York
jaw2016@med.cornell.edu
Nutritional Support (in Chapter 29)

Judith Walsh, MD, MPH
Professor of Clinical Medicine, Division of General Internal Medicine, Women's Health Center of Excellence, University of California, San Francisco
Judith.Walsh@ucsf.edu
CMDT Online—Women's Health Issues

Thomas J. Walsh, MD, MS
Professor of Urology, Department of Urology, University of Washington School of Medicine, Seattle, Washington
walsht@uw.edu
Urologic Disorders

Sunny Wang, MD
Professor of Clinical Medicine, Division of Hematology/Oncology, University of California, San Francisco; Chief of Hematology/Oncology, San Francisco Veterans Affairs Health Care System
sunny.wang@ucsf.edu
Cancer

Nolan R. Williams, MD
Assistant Professor of Psychiatry and Behavioral Sciences, Department of Psychiatry; Director of Brain Stimulation Laboratory, Stanford University School of Medicine, Stanford, California
nolanw@stanford.edu
Psychiatric Disorders

Leah J. Witt, MD
Assistant Professor, Division of Geriatrics and Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Department of Medicine, University of California, San Francisco
Leah.Witt@ucsf.edu
Geriatric Disorders

Tyler B. Woodell, MD, MCR
Assistant Professor of Medicine, Division of Nephrology-Hypertension, Department of Medicine, University of California, San Diego
twoodell@ucsd.edu
Kidney Disease

Jinoos Yazdany, MD, MPH
Alice Betts Endowed Professor, Department of Medicine, University of California, San Francisco; Chief of Division of Rheumatology, Zuckerberg San Francisco General Hospital
Jinoos.Yazdany@ucsf.edu
Rheumatologic, Immunologic, & Allergic Disorders

Preface

Current Medical Diagnosis & Treatment 2023 (CMDT 2023) is the 62nd edition of this single-source reference for practitioners of adult medicine in both hospital and ambulatory settings. The book emphasizes the practical features of clinical diagnosis and patient management in all fields of internal medicine and in specialties of interest to primary care practitioners and to subspecialists who provide general care.

With a growing recognition of systemic racism and other biases in institutions across our societies, including the institution of medicine (https://www.mdcalc.com/race), the editors of *CMDT,* with humility, have committed to a thorough examination of our content to remove biased language, research, and recommendations. Since 2020, we have been pursuing an ongoing, formal process of review and revision in an effort to recognize and correct biases and to promote equity in our book and the practice of medicine. While we, the editors, take this on as our responsibility, we also invite readers to share with us any *CMDT* content that they find problematic or biased.

We have tried to describe populations used in the studies that form the basis of the information in *CMDT,* use appropriate language where we can (eg, persons of sub-Sahara African descent, rather than African-Americans), and use the gender-neutral term Latinx. We acknowledge that, like others,[1] we find this an imperfect solution. We continue, however, to use terms from original sources when study populations are broad.

INTENDED AUDIENCE FOR *CMDT*

House officers, medical students, and all other health professions students will find the descriptions of diagnostic and therapeutic modalities, with citations to the current literature, of everyday usefulness in patient care.

Internists, family physicians, hospitalists, nurse practitioners, physician assistants, and all primary care providers of adult medicine will appreciate *CMDT* as a ready reference and refresher text. Physicians in other specialties, pharmacists, and dentists will find the book a useful basic medical reference text. Nurses, nurse practitioners, and physician assistants will welcome the format and scope of the book as a means of quickly referencing medical diagnosis and treatment modalities.

Patients and their family members who seek information about the nature of specific diseases and their diagnosis and treatment may also find this book to be a valuable resource.

NEW IN THIS EDITION OF *CMDT*

- INNOVATIVE TABLE highlighting the **"Year in Review: Key Clinical Updates in *CMDT 2023*,"** individually listed with page numbers and reference citations, for easy access to significant changes in this edition
- Ongoing concerted effort to address and remove unconscious bias
- List of Common Abbreviations used in *CMDT* can be found on the inside of the front cover
- New section on opioids for pain management
- Overhauled organization of Dermatology chapter to better reflect categorization of conditions and lesions
- Expanded section of interventional therapies to manage chronic pain
- Updated USPSTF lung cancer screening recommendations using low-dose CT
- New prognostic systems for primary myelofibrosis: GIPSS and MIPSSv2
- Discussion of the use of DOACs in patients with morbid obesity who require antithrombotic therapy
- Updated section on osmotic laxatives to treat chronic constipation
- Ozanimod approved for the treatment of moderate to severe ulcerative colitis
- Landmark change in staging female breast carcinoma modifying anatomic stage and adding prognostic stage
- New medications for treating metastatic breast cancer (olaparib, talazoparib, palbociclib, ribociclib, and abemaciclib)
- New recommendations on treating cholestasis of pregnancy
- Updated criteria for diagnosing systemic lupus erythematosus to include antinuclear antibody measurement
- New medications for active lupus nephritis, including voclosporin used with mycophenolate mofetil as well as belimumab
- Anifrolumab is approved for nonrenal lupus when standard therapies fail

[1]April 2021 Annals of Internal Medicine: A Comprehensive Policy Framework to Understand and Address Disparities and Discrimination in Health and Health Care: A Policy Paper From the American College of Physicians. Appendix 2: Glossary.

- New guidelines for diagnosing polyarteritis nodosa
- New American College of Rheumatology/Vasculitis Foundation recommendations for the treatment of granulomatosis with polyangiitis
- A newly described genetic syndrome, VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) in the differential diagnosis of relapsing polychondritis
- Discussion of the role of left atrial appendage closure in preventing stroke and systemic embolization
- Aducanumab (anti-amyloid therapy) is approved by the US FDA for the treatment of Alzheimer disease
- Extensive revision of the Thyroiditis section in Endocrine Disorders chapter
- Substantial revision of the Nutritional Support section in the Nutritional Disorders & Obesity chapter
- Substantial revision in the HIV Infection & AIDS chapter, including updates in the available therapeutic regimens
- Rewritten SARS-CoV-2 section and inclusion of SARS-CoV-2 information relevant to specific chapters throughout the textbook
- Extensive revision of Sexual & Gender Minority Health chapter, including sections on family planning and health care for transgender and gender diverse persons

OUTSTANDING FEATURES OF *CMDT*

- Medical advances up to time of annual publication
- Detailed presentation of internal medicine disciplines, plus primary care topics in gynecology, obstetrics, dermatology, ophthalmology, otolaryngology, psychiatry, neurology, toxicology, urology, geriatrics, orthopedics, women's health, sexual and gender minority health, preventive medicine, and palliative care
- Concise format, facilitating efficient use in any practice setting
- More than 1000 diseases and disorders
- Specific disease prevention information
- Easy access to medication dosages, with trade names indexed and current costs updated in each annual edition
- Recent references, with unique identifiers (PubMed, PMID numbers) for rapid downloading of article abstracts and, in some instances, full-text reference articles

E-CHAPTERS, *CMDT ONLINE*, & AVAILABLE APPS

Seven ***e-chapters*** listed in the Table of Contents can be accessed at **www.AccessMedicine.com/CMDT.** These online-only chapters (available without need for subscription) include

- Anti-Infective Chemotherapeutic & Antibiotic Agents
- Diagnostic Testing & Medical Decision Making
- Information Technology in Patient Care
- Integrative Medicine
- Podiatric Disorders
- Women's Health Issues
- Appendix: Therapeutic Drug Monitoring, Laboratory Reference Intervals, & Commonly Used Blood Specimen Collection Tubes

Institutional or individual subscriptions to AccessMedicine also have full electronic access to *CMDT 2023*. Subscribers to ***CMDT Online*** receive full electronic access to *CMDT 2023* as well as

- An expanded, dedicated media gallery; new to this edition are educational videos and printable protocols in the Orthopedic Disorders & Sports Medicine chapter
- ***Quick Medical Diagnosis & Treatment***—a concise, bulleted version of *CMDT 2023*
- ***Guide to Diagnostic Tests***—for quick reference to the selection and interpretation of commonly used diagnostic tests
- ***CURRENT Practice Guidelines in Primary Care***—delivering concise summaries of the most relevant guidelines in primary care
- ***Diagnosaurus***—consisting of 1000+ differential diagnoses

CMDT 2023, QMDT, *Guide to Diagnostic Tests*, and *Diagnosaurus* are also available as individual apps for your smartphone or tablet and can be found in the Apple App Store and Google Play.

SPECIAL RECOGNITION: MITCHELL H. KATZ, MD

With this 2023 edition of *CMDT*, we express our immense gratitude and say goodbye to Mitchell H. Katz, MD as he transitions away from his 30+ years as author of Chapter 31 "HIV Infection & AIDS."

A graduate of Yale College and Harvard Medical School, Dr. Katz completed his residency in the UCSF Primary Care General Internal Medicine Residency, and then trained as a Robert Wood Johnson Clinical Scholar.

Dr. Katz has spent the bulk of his career in public service. He began his work in 1991 in the San Francisco Department of Public Health, ultimately being appointed Director and Health Officer of the Department of Health. He was probably best known for funding San Francisco's successful needle exchange program; for creating its "Healthy San Francisco" Program as the first comprehensive municipal health care and financing system in the United States; for outlawing the sale of tobacco at pharmacies; and for winning ballot measures funding the replacement of the City's 780-bed nursing home, the Laguna Honda Hospital & Rehabilitation Center, and for rebuilding its 386-bed public "safety net" hospital, the Zuckerberg San Francisco General Hospital.

In 2010, Dr. Katz was appointed the Director of the Los Angeles County Department of Health Services (DHS), the second largest public safety net system in the U.S. While in L.A., he created an ambulatory care network that empaneled over 350,000 patients in a primary care home and that transitioned over 4000 medically complex patients from care at hospitals and emergency departments into independent housing, effectively eliminating unnecessary and expensive hospital care and giving these patients the dignity of their own home.

Moving to New York City in 2018, Dr. Katz became President and CEO of NYC Health and Hospitals, the largest municipal health system in the U.S. He is the architect of NYC Care, a health access program that provides comprehensive health care to New Yorkers regardless of income or immigration status. In the spring of 2019, Dr. Katz steered the municipal health system through the worst of the COVID-19 outbreak when NYC was the epicenter of the U.S. pandemic. In a 6-week period, he tripled the number of ICU beds to care for acutely ill patients.

Dr. Katz is an elected member of the National Academy of Sciences and is the Deputy Editor of *JAMA Internal Medicine*. He has published extensively in the areas of HIV epidemiology and health care access. He practices as a primary care physician at Gouverneur Health in Manhattan. Mitch and his partner, Rabbi Igael Gurin-Malous, have two children, Maxwell and Roxie, who were adopted from an orphanage in Vietnam.

As Mitch's editors, we are particularly thankful for his expert annual submissions, providing us a precis about the care of patients with HIV infection/AIDS. We are immensely grateful for his friendship and look forward to hearing about the next chapters in his amazing career of service.

ACKNOWLEDGMENTS

We wish to thank our authors for participating once again in the annual updating of this important book. We are especially grateful to N. Franklin Adkinson, Jr., MD, Antoine Azar, MD, Thomas M. Bashore, MD, C. Seth Landefeld, MD, Manesh R. Patel, MD, George R. Schade, MD, Joshua S. Schindler, MD, and Scott Steiger, MD who are leaving *CMDT* this year. We have all benefited from their clinical wisdom and commitment.

With enormous gratitude and respect, we dedicate this 62nd edition of *Current Medical Diagnosis & Treatment* to all health care professionals and staff who have cared for patients with COVID-19. We honor their competence, their humanity, and their bravery. We also wish to extend our heartfelt gratitude to Eva Clark, MD, PhD, and to Wayne Shandera, MD, for coauthoring (along with Christine Akamine, MD) the authoritative section on COVID-19 (SARS-CoV-2) in the Viral chapter of the print edition of *CMDT* and for providing ongoing, current, and expert updates on this topic in *CMDT Online*.

Many students and physicians have contributed useful suggestions to this and previous editions, and we are grateful. We continue to welcome comments and recommendations for future editions in writing or via electronic mail. The editors' e-mail addresses are below, and author e-mail addresses are included in the Authors section.

Maxine A. Papadakis, MD — Maxine.Papadakis@ucsf.edu
Stephen J. McPhee, MD — Stephen.McPhee@ucsf.edu
Michael W. Rabow, MD — Mike.Rabow@ucsf.edu
Kenneth R. McQuaid, MD — Kenneth.McQuaid@ucsf.edu

San Francisco, California

Dedication

Harriet Lebowitz

The editors and publishers of *Current Medical Diagnosis & Treatment* (*CMDT*) wish to dedicate this 62nd edition of *CMDT* to Harriet Lebowitz, in recognition of her more than 20 years of service as our Senior Project Development Editor. Harriet, who is retiring with this edition, has been the major organizing force responsible for the annual production of *CMDT*.

In particular, we would like to express our gratitude to Harriet for her dedication in making *CMDT* the world's number one best-selling annually updated medical textbook in print, online, app, and abbreviated formats (*Quick Medical Diagnosis & Treatment*). Among other innovations that Harriet has contributed, she most recently envisioned and helped create *CMDT's* "Year in Review: Key Clinical Updates" feature.

Throughout many changes over the years, Harriet has been a constant positive presence. Her familiarity with the text, editors, and authors as well as all the arcane details of publishing helped guide our journey to an on-time publication each year. We will all miss working with Harriet very much and wish her the absolute best in her retirement.

YEAR IN REVIEW: KEY CLINICAL UPDATES IN CMDT 2023

Topic	Page Number	Key New Advances Affecting Clinical Practice*
CHAPTER 2: COMMON SYMPTOMS		
Dyspnea	19	• Point-of-care ultrasonography (POCUS) consistently improved the sensitivities of standard diagnostic pathways to detect heart failure, pneumonia, PE, pleural effusion, or pneumothorax. Specificities increased in most, but not all, studies; in-hospital mortality and length of hospital stay, however, did not differ significantly between patients who did or did not receive POCUS in addition to standard diagnostic tests. *Gartlehner G et al. Ann Intern Med. [PMID: 33900798]*
Dysuria	41	• A systematic review and meta-analysis found D-mannose protective against recurrent UTIs. *Lenger SM et al. Am J Obstet Gynecol. [PMID: 32497610]*
Fatigue & Systemic Intolerance Disease (Chronic Fatigue Syndrome)	34	• Pitolisant, a selective histamine H3-receptor antagonist with wake-promoting effect, may reduce daytime sleepiness in patients with moderate to severe obstructive sleep apnea who do not want continuous positive airway pressure treatment. *Dauvilliers Y et al. Am J Respir Crit Care Med. [PMID: 31917607]*
CHAPTER 4: GERIATRIC DISORDERS		
Dementia	55	• Aducanumab, a monoclonal antibody that targets amyloid-beta protein and promotes its clearance from the brain, became the first new drug approved by the FDA for the treatment of Alzheimer disease since 2003. However, its role in routine clinical care remains unclear. *Lin GA et al. https://icer.org/assessment/alzheimersdisease-2021/*
CHAPTER 7: DISORDERS OF THE EYES & LIDS		
Optic Neuritis	194	• Newer therapies include monoclonal antibodies against immune cells and cell-based therapies to deplete or modulate T- and B-cell responses. *Derdelinckx J et al. Int J Mol Sci. [PMID: 34360690]*
CHAPTER 8: OTOLARYNGOLOGY DISORDERS		
Bacterial Rhinosinusitis	220	• Dupilumab, a monoclonal antibody with inhibition of IL-4 and IL-13, is FDA-approved for patients with chronic sinusitis with nasal polyposis. *Hoy SM. Drugs. [PMID: 32240527]*
Sensorineural Hearing Loss	212	• There is emerging evidence that conventional audiometry may not fully capture hearing loss (known as "hidden hearing loss"). Many patients may have subclinical hearing loss. *Drennan WR. Audiol Neurootol. [PMID: 34727540]*
CHAPTER 9: PULMONARY DISORDERS		
Allergic Bronchopulmonary Aspergillosis	266	• For patients with frequent exacerbations, the use of biologic agents, such as anti-IgE (omalizumab), anti-IL-5 (mepolizumab, benralizumab), or anti-IL4 receptor (dupilumab), has been shown to improve outcomes. *Koutsokera A et al. J Cyst Fibros. [PMID: 31405730]*
Bronchial Carcinoid Tumors	291	• The aggressiveness of bronchial carcinoid tumors is determined by the cell histology, with "typical carcinoid," a low-grade tumor, demonstrating a more indolent and favorable course than "atypical carcinoid," an intermediate-grade tumor. Bronchial carcinoid tumor staging follows the same TNM classification as other lung cancers. *Singh S et al. J Thorac Oncol. [PMID: 32663527]*

*See chapter for further details and references.

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Topic	Page Number	Key New Advances Affecting Clinical Practice*
Screening for Lung Cancer	289	• The USPSTF updated its recommendation for low-dose CT screening. Annual low-dose CT screening for lung cancer is recommended for those at high risk; with high-risk criteria including age 50–80 years, at least a 20 pack-years smoking history, and either current smoking or quit date within past 15 years. Screening should be stopped once 15 years have elapsed since quitting smoking, or if a comorbid condition renders the benefits of screening null. Simulation models developed for the purposes of informing this recommendation found yearly screening with these parameters to be the most efficient in reducing lung-cancer related deaths, although more false-positive test results are expected compared with the original recommendation. *Krist AH et al. JAMA. [PMID: 33687470]*
CHAPTER 10: HEART DISEASE		
Chronic Stable Angina Pectoris (Chronic Coronary Syndromes)	361	• CT-functional fractional reserve (CT-FFR) is approved for clinical use and is endorsed with a level IIa recommendation for intermediate-risk patients with chest pain and no prior history of CAD with a 40–90% stenosis on CT imaging to guide need for revascularization. *Writing Committee Members; Gulati M et al. J Am Coll Cardiol. [PMID: 34756653]*
Heart Failure	408, 409	• The FDA approved sacubitril/valsartan in patients with heart failure and preserved LVEF, particularly for patients with an EF less than 50%, including patients with a mildly reduced EF of 41–49%. • Empagliflozin has been FDA-approved to treat heart failure with reduced LVEF, with or without diabetes; it is the only therapy shown to reduce cardiovascular death or heart failure hospitalization in this population. *McDonagh TA et al. Eur J Heart Fail. [PMID: 35083827]* *Bozkurt B et al. J Card Fail. [PMID: 33663906]*
Infectious Myocarditis	414	• Myocarditis following infection with SARS-CoV-2 infection and following vaccination have been reported in the medical literature. In both scenarios, younger male patients seem to be at highest risk for this overall rare event. *Boehmer TK et al. MMWR Morb Mortal Wkly Rep. [PMID: 34473684]* *Witberg G et al. N Engl J Med. [PMID: 34614329]*
Primary & Secondary Prevention of CHD	358	• The USPSTF issued new guidance on the use of aspirin for primary prevention of cardiovascular events; patients aged 40–49 years should have a shared decision-making conversation regarding the potential risks and benefits of initiating aspirin therapy for primary prevention, and patients aged 60 years or older should not initiate aspirin for primary prevention of CVD. *USPSTF.* *https://www.uspreventiveservicestaskforce.org/uspstf/sites/default/files/file/supporting_documents/aspirin-cvd-prevention-final-rec-bulletin.pdf*
CHAPTER 11: SYSTEMIC HYPERTENSION		
Systemic Hypertension	465	• Most guidelines now recommend the use of home blood pressure monitors in the diagnosis of hypertension. The availability of blood pressure profiles generated from multiple home-gathered data points over continuous intervals allows more precise control of the overall hypertensive burden. *Milani RV et al. Curr Opin Cardiol. [PMID: 33871402]*
CHAPTER 12: BLOOD VESSEL & LYMPHATIC DISORDERS		
Aortic Dissection	487	• For patients who cannot tolerate a beta-blocker or who need a second agent to control hypertension, intravenous calcium channel blocker infusions such as nicardipine are an alternative. Start nicardipine 5 mg/hour intravenously and titrate the infusion to the desired effect. *Bossone E et al. Nat Rev Cardiol. [PMID: 33353985]*
Occlusive Disease: Femoral & Popliteal Arteries	475	• Dual treatment with rivaroxaban 2.5 mg orally twice daily and aspirin 81 mg orally daily has been shown to reduce limb-related events, major amputation, and cardiovascular events in patients with femoral and popliteal artery atherosclerosis. *Bauersachs RM et al. J Am Coll Cardiol. [PMID: 34010631]*

*See chapter for further details and references.

Topic	Page Number	Key New Advances Affecting Clinical Practice*
CHAPTER 13: BLOOD DISORDERS		
Plasma Cell Myeloma	538	• For patients with multi-agent refractory disease, chimeric antigen receptor T-cell therapy targeting the early plasma cell antigen BCMA has shown response rates exceeding 70% and median duration of response of over 11 months. *van de Donk NWCJ et al. Lancet Haematol. [PMID: 34048683]*
CHAPTER 14: DISORDERS OF HEMOSTASIS, THROMBOSIS & ANTITHROMBOTIC THERAPY		
Antithrombotic Therapy	563	• For patients with morbid obesity, standard doses of apixaban or rivaroxaban should be chosen rather than using dabigatran or edoxaban. • DOACs are not recommended for VTE treatment in the acute setting following bariatric surgery but can be considered for ongoing treatment after the initial 4 weeks of therapy.
	571	• Heparins may be preferable as initial therapy in hospitalized patients with clinical instability and fluctuating renal or hepatic function, when bleeding risk is high, or when there is concern that thrombolysis may be required. *Stevens SM et al. Chest. [PMID: 34352278]*
Primary VTE Prevention & Treatment in Severe COVID-19	578	• Therapeutic dosing of anticoagulation may benefit some patients who are hospitalized in the acute care setting with COVID-19, who have very elevated D-dimer values and require supplemental oxygen, and who have low bleeding risk. • Patients who are critically ill in ICUs have not been shown to benefit from therapeutic dosing of anticogulation. • There is no clear benefit from VTE prophylaxis for patients with COVID-19 who do not require hospitalization. *ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators; Lawler PR et al. N Engl J Med. [PMID: 34351721]* *REMAP-CAP Investigators; ACTIV-4a Investigators; ATTACC Investigators; Goligher EC et al. N Engl J Med. [PMID: 34351722]* *Spyropoulos AC. JAMA Intern Med. [PMID: 34617959]*
CHAPTER 15: GASTROINTESTINAL DISORDERS		
Acute Diarrhea	591	• Immune checkpoint inhibitor therapy for malignancies may cause mild to severe GI side effects in 8–27% of patients. *Dougan M et al. Gastroenterology. [PMID: 33080231]* *Siciliano V et al. Rev Recent Clin Trials. [PMID: 32598272]*
	592	• Patients with severe diarrhea or dysentery and a known history of IBD or prior immune checkpoint inhibitor therapy require expedited evaluation with stool studies and possible sigmoidoscopy or colonoscopy with biopsy to exclude infection prior to therapy with intravenous corticosteroids. • Shiga-toxin–producing *Escherichia coli* infection should not be treated with antibiotics due to an increased risk of hemolytic-uremic syndrome, especially in children. *Dougan M et al. Gastroenterology. [PMID: 33080231]* *Siciliano V et al. Rev Recent Clin Trials. [PMID: 32598272]*
Anorectal Infections	670	• Nucleic acid amplification testing for gonorrhea and chlamydia has excellent sensitivity and specificity and is preferred in most clinical settings. *Workowski KA et al. MMWR Recomm Rep. [PMID: 34292926]*
Chronic Diarrhea	594	• Elevated fasting levels (> 48 ng/mL) of the bile acid precursor 7αC4 are strongly predictive of bile acid diarrhea. *Borup C et al. Am J Gastroenterol. [PMID: 32740083]*
Gastrointestinal Hemorrhage	630	• Endoscopic application of a topical hemostatic powder (Hemospray) may provide temporary hemostasis for up to 24 hours in patients with massive bleeding that interferes with effective application of thermocoagulation or endoclip placement. *Hussein M et al. Endoscopy. [PMID: 32459010]*
Inflammatory Bowel Disease	651	• Ozanimod is FDA-approved for the treatment of moderate to severe ulcerative colitis. *Sandborn WJ et al. N Engl J Med. [PMID: 34587385]*

*See chapter for further details and references.

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Topic	Page Number	Key New Advances Affecting Clinical Practice*
Irritable Bowel Syndrome (IBS)	646	• Peppermint oil may be useful to relieve global IBS symptoms and abdominal pain. *Lacy BE et al. Am J Gastroenterol. [PMID: 33315591]*
	647	• Probiotics are not recommended for IBS treatment. *Lacy BE et al. Am J Gastroenterol. [PMID: 33315591]*
Other Primary Esophageal Motility Disorders	620	• Opioids may exacerbate esophageal dysmotility and should be discontinued, if possible. No medications have been shown to improve symptoms in patient with esophageal hypomotility. *DeLay K et al. Clin Gastroenterol Hepatol. [PMID: 34405804]*
Peptic Ulcer Disease	627	• Commercial laboratories now offer culture-based and molecular-based susceptibility testing for *Helicobacter pylori*, which may be helpful for patients who have failed an initial empiric course of treatment. *Graham DY. Gastroenterology. [PMID: 33647279]*
Zenker Diverticulum	615	• Minimally invasive intraluminal approaches that use flexible endoscopes or rigid esophagoscopes are preferred when symptomatic patients require cricopharyngeal myotomy. *Jirapinyo P et al. Gastrointest Endosc. [PMID: 33926711]*
CHAPTER 16: LIVER, BILIARY TRACT, & PANCREAS DISORDERS		
Cirrhosis	702	• In patients with clinically significant portal hypertension, carvedilol, a nonselective beta-receptor antagonist with alpha-1 blocking activity, appears to reduce the frequency of decompensating events, although it may lead to hypotension particularly in patients with decompensated cirrhosis. *Tandon P et al. Clin Gastroenterol Hepatol. [PMID: 33221550]*
	703	• Vancomycin should be added in patients with prior bacterial peritonitis or a positive surveillance swab for methicillin-resistant *Staphylococcus aureus*. Daptomycin should be added in patients with a positive surveillance swab for vancomycin-resistant enterococcus. Meropenem can be used in patients with current or recent exposure to piperacillin-tazobactam. *Biggins SW et al. Hepatology. [PMID: 33942342]*
Hemochromatosis	710	• Serum biomarkers of fibrosis may be an alternative to liver biopsy for identifying advanced fibrosis. *Chin J et al. Clin Gastroenterol Hepatol. [PMID: 32745684]*
Nonalcoholic Fatty Liver Disease	698	• Noninvasive approaches to the assessment of fibrosis are now preferred, with liver biopsy reserved when results of noninvasive testing are inconclusive. The FIB-4 score is often used particularly to exclude advanced fibrosis because of its simplicity. It is based on age, platelet count, and serum AST and ALT levels. *Younossi ZM et al. Am J Gastroenterol. [PMID: 33284184]*
Primary Biliary Cholangitis	708	• Obeticholic acid, a farnesoid X receptor agonist, can cause serious liver injury in patients with advanced cirrhosis, and its use in these patients has been restricted by the FDA. *Lleo A et al. Lancet. [PMID: 33308474]*

*See chapter for further details and references.

Topic	Page Number	Key New Advances Affecting Clinical Practice*
CHAPTER 17: BREAST DISORDERS		
Carcinoma of the Female Breast	752	• Olaparib has been shown to reduce the relative risk of an invasive recurrence for *BRCA1/2* carriers with high-risk disease; abemaciclib has been shown to improve the invasive disease-free survival for those with high-risk HR-positive disease; pembrolizumab has been shown to improve the event-free survival for patients with stage II or greater triple-negative breast cancer. *Schmid P et al; KEYNOTE-522 Investigators. N Engl J Med. [PMID: 32101663]* *Tutt ANJ et al; OlympiA Clinical Trial Steering Committee and Investigators. N Engl J Med. [PMID: 34081848]*
	754	• Hormonally driven breast cancer may be particularly sensitive to inhibition of cell cycle regulatory proteins, called cyclin dependent kinases 4 and 6 (CDK 4/6). Three oral CDK4/6 inhibitors—palbociclib, ribociclib, and abemaciclib—are FDA-approved for treatment of HR-positive, HER2-negative metastatic breast cancer. • Two poly(ADP-ribose) polymerase (PARP) inhibitors (olaparib and talazoparib) are FDA-approved for the treatment of BRCA-associated metastatic breast cancer. The NCCN guidelines include adjuvant olaparib for select patients and recommend germline genetic testing for any patient who may be a candidate for adjuvant olaparib. *Schmid P et al; KEYNOTE-522 Investigators. N Engl J Med. [PMID: 32101663]* *Tutt ANJ et al; OlympiA Clinical Trial Steering Committee and Investigators. N Engl J Med. [PMID: 34081848]*
CHAPTER 18: GYNECOLOGIC DISORDERS		
Intrauterine Devices	778	• The levonorgestrel 52-mg intrauterine device can be inserted within 5 days following a single episode of unprotected midcycle coitus as a postcoital contraceptive. *Turok DK et al. N Engl J Med. [PMID: 33503342]*
Pelvic Inflammatory Disease (Salpingitis, Endometritis)	786	• The recommended outpatient regimen is ceftriaxone (500 mg intramuscularly; 1 g for persons who weigh 150 kg or greater) plus doxycycline (100 mg orally twice a day for 14 days) with metronidazole 500 mg orally twice a day or a single dose of cefoxitin (2 g intramuscularly) with probenecid (1 g orally) plus doxycycline (100 mg orally twice daily for 14 days) and metronidazole 500 mg orally twice daily for 14 days. *Workowski KA et al. MMWR Recomm Rep. [PMID: 34292926]*
CHAPTER 19: OBSTETRICS & OBSTETRIC DISORDERS		
Cholelithiasis & Cholecystitis	817	• The most common cause of acute pancreatitis in pregnancy is gallstone disease. The diagnosis can be confirmed with an appropriate history and an elevated serum amylase or lipase. Management is conservative, including bowel rest, intravenous fluids, supplemental nutrition if necessary, and analgesics. CT imaging should be avoided unless severe complications are suspected. *Abushamma S et al. Obstet Gynecol. [PMID: 34011887]*
Immunizations During Pregnancy	795	• Vaccination against COVID-19 is recommended for women who are pregnant, trying to get pregnant or may become pregnant, and who are breastfeeding. The CDC has determined that the benefits of vaccination outweigh any risks. There is no evidence that vaccination causes problems with fertility in men or women. Pregnant women who have been vaccinated may receive the COVID-19 booster shot. There have been rare reports of thrombosis with thrombocytopenia syndrome in women younger than 50 years old who received the Johnson and Johnson's Janssen vaccine. This risk has not been found with the Pfizer-BioNTech and Moderna vaccines; women younger than 50 years old with access to multiple vaccines may want to factor this into their decision-making process. *CDC. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html*
Maternal Hepatitis B & C Carrier State	816	• Universal screening for hepatitis C virus in pregnancy is recommended. Direct-acting antiviral regimens should only be initiated during pregnancy if in the setting of a clinical trial. Cesarean section is not recommended solely for a maternal history of hepatitis C. During labor, early rupture of membranes and placement of a fetal scalp electrode should be avoided if safe to do so. *Dotters-Katz SK et al. Am J Obstet Gynecol. [PMID: 34116035]*

*See chapter for further details and references.

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Topic	Page Number	Key New Advances Affecting Clinical Practice*
Preterm Labor	805	• The recommended regimen for antimicrobial prophylaxis against group B streptococcus is penicillin G, 5 million units intravenously as a loading dose and then 2.5–3 million units intravenously every 4 hours until delivery. In penicillin-allergic patients not at high risk for anaphylaxis, 2 g of cefazolin can be given intravenously as an initial dose and then 1 g intravenously every 8 hours until delivery. In patients at high risk for anaphylaxis, vancomycin, 20 mg/kg intravenously every 8 hours until delivery, can be used. Clindamycin, 900 mg intravenously every 8 hours until delivery, can also be used after a group B streptococcal isolate has been confirmed to be susceptible to clindamycin. *American College of Obstetricians and Gynecologists. Obstet Gynecol. [PMID: 34794160]*
CHAPTER 20: RHEUMATOLOGIC, IMMUNOLOGIC, & ALLERGIC DISORDERS		
Complex Regional Pain Syndrome	867	• Vitamin C supplementation may have a role in preventing the development of complex regional pain syndrome following surgical procedures known to be a risk factor. *Jacques H et al. Int Orthop. [PMID: 33438072]*
Gonococcal Arthritis	863	• The treatment of disseminated gonorrhea is parenteral ceftriaxone. Once susceptibility testing has been obtained, 24–48 hours after clinical improvement the antibiotic regimen can be changed to an oral agent to complete a 7-day course. *CDC. https://www.cdc.gov/std/treatment-guidelines/gonorrhea-adults.htm*
Granulomatosis with Polyangiitis	853	• American College of Rheumatology/Vasculitis Foundation recommendations favor rituximab as first-line induction therapy. Cyclophosphamide may also be used for induction therapy. Avacopan is FDA-approved as add-on treatment for severe ANCA-associated vasculitis induction therapy in combination with rituximab or cyclophosphamide plus corticosteroids. • For nonsevere disease without life- or organ-threatening manifestations, methotrexate up to 25 mg oral or subcutaneous weekly plus corticosteroids may be effective induction therapy. • Rituximab, dosed at a fixed interval of 1 g every 6 months or 500 mg every 4 months, is favored as first-line maintenance treatment. *Chung SA et al. Arthritis Rheumatol. [PMID: 34235894]* *Jayne DRW et al; ADVOCATE Study Group. N Engl J Med. [PMID: 33596356]*
Polyarteritis Nodosa	851	• High-dose pulse methylprednisolone is recommended as the initial treatment for severe polyarteritis nodosa. *Chung SA et al. Arthritis Rheumatol. [PMID: 34235883]*
Relapsing Polychondritis	856	• A newly described genetic syndrome, VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic), is caused by somatic mutations in *UBA1* in hematopoietic progenitor cells. Clinical features include hematologic manifestations (cytopenias, bone marrow failure) and a spectrum of inflammatory features such as chondritis, vasculitis, fever, and arthritis. This rare syndrome (predominately in males because it is X-linked) should be considered in the differential diagnosis of chondritis especially in the presence of an unexplained macrocytosis and evidence of systemic inflammation (ie, high ESR/CRP). *Ferrada MA et al. Arthritis Rheumatol. [PMID: 33779074]*
Rheumatoid Arthritis	831	• Because rituximab reduces the humoral immune response, it should be used with caution during the COVID-19 pandemic as multiple studies suggest a higher risk of mortality from COVID-19 in patients using this medication. *Fraenkel L et al. Arthritis Care Res (Hoboken). [PMID: 34101387]*
Systemic Lupus Erythematosus	835–836	• Belimumab is FDA-approved for the treatment of active lupus nephritis. • Anifrolumab, a type 1 interferon receptor antagonist, is FDA-approved to treat non-renal lupus that has not responded to standard therapies. • Voclosporin, a novel calcineurin inhibitor, is FDA-approved to treat active lupus nephritis when used in combination with mycophenolate mofetil. • Evidence increasingly suggests that renal response can be enhanced with combination immunosuppressive therapy. *Morand EF et al; TULIP-2 Trial Investigators. N Engl J Med. [PMID: 31851795]* *Rovin BH et al. Lancet. [PMID: 33971155]*

*See chapter for further details and references.

Topic	Page Number	Key New Advances Affecting Clinical Practice*
Systemic Sclerosis (Scleroderma)	841	• Tocilizumab, an IL-6 inhibitor, slows the rate of decline in pulmonary function and may be used as an alternative for patients who cannot tolerate mycophenolate mofetil. Azathioprine is an additional option for treatment of systemic sclerosis–associated lung disease. *Khanna D et al; focuSSced Investigators. Lancet Respir Med. [PMID: 32866440]*
CHAPTER 21: ELECTROLYTE & ACID-BASE DISORDERS		
Hyperkalemia	886	• Small studies have suggested the utility of patiromer and sodium zirconium cyclosilicate in acute hyperkalemia; if administered for hyperkalemic emergency, sodium zirconium cyclosilicate is preferred due to its more rapid onset of action. *Rafique Z et al. Acad Emerg Med. [PMID: 31599043]* *Peacock WF et al. Acam Emerg Med. [PMID: 32149451]*
CHAPTER 22: KIDNEY DISEASE		
Diabetic Nephropathy	935	• Mineralocorticoid receptor antagonism can be considered for blood pressure and proteinuria management in type 2 diabetes mellitus with careful monitoring for hyperkalemia. *Hahr AJ et al. Am J Kidney Dis. [PMID: 34600745]*
IgA Nephropathy	927	• SGLT2-inhibitors may be added to standard care in the well-selected patient. There are conflicting data regarding the efficacy of corticosteroids for reducing proteinuria and slowing progression; however, they may be considered for patients with GFR greater than 30 mL/ minute/1.73 m^2 and persistent proteinuria greater than 1 g/day despite maximal ACE inhibitor or ARB. *Cheung CK et al. J Clin Med. [PMID: 34200024]*
CHAPTER 24: NERVOUS SYSTEM DISORDERS		
Dementia	1016	• Aducanumab was approved by the FDA despite mixed results in clinical trials. Its use is limited to patients with mild cognitive impairment or mild dementia and amyloid pathology proven by amyloid PET. The ultimate role of this medication is still being debated.
Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)	1005	• Weight loss is important: bariatric surgery led to a decrease in both intracranial pressure and weight at 2 years compared with a community weight management program in a randomized trial and may be considered in patients with a BMI of 35 or greater. *Mollan SP et al. JAMA Neurol. [PMID: 33900360]*
Metastatic Intracranial Tumors	1001	• Memantine (5 mg once daily orally titrated by 5 mg weekly to 10 mg twice daily) reduced cognitive toxicity associated with whole-brain radiotherapy in a randomized trial and is recommended; this effect can be augmented through intensity modulated radiation therapy with hippocampal avoidance. *Brown PD et al. J Clin Oncol. [PMID: 32058845]*
Muscular Dystrophies	1044	• Casimersen is FDA-approved for treatment of Duchenne muscular dystrophy; it shows benefit in patients with a mutation amenable to exon 45 skipping.
Transient Ischemic Attack (TIA)	987	• Dual antiplatelet therapy with aspirin and clopidogrel is recommended for 90 days after a TIA or stroke due to 70–99% stenosis of an intracranial artery. • The left atrial appendage is the source of embolism in most patients with atrial fibrillation. Several randomized trials showed percutaneous left atrial appendage closure was equivalent to anticoagulation in preventing stroke and systemic embolization, and several devices are approved for this indication in the United States and Europe. The procedure should be considered in patients with a contraindication to long-term anticoagulation, although short-term anticoagulation (45 days) followed by dual antiplatelet therapy (4.5 months) and then indefinite aspirin monotherapy is usually necessary after device placement. *Kleindorfer DO et al. 2021 Stroke. [PMID: 34024117]*
CHAPTER 25: PSYCHIATRIC DISORDERS		
Psychosexual Disorders	1059	• Bremelanotide is FDA-approved for the treatment of hypoactive sexual desire disorder in premenopausal women; however, the mechanism of action is unclear and subjective improvement is low. *Wheeler LJ et al. Obstet Gynecol. [PMID: 32541291]*

*See chapter for further details and references.

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Topic	Page Number	Key New Advances Affecting Clinical Practice*
Somatic Symptom Disorders (Abnormal Illness Behavior)	1055	• Physical-based therapies such as speech/occupational/physical have strong evidence for improving symptoms in those suffering from functional neurologic disorder. *Gilmour GS et al. J Neurol. [PMID: 32193596]*
Trauma & Stressor-related Disorders	1048	• MDMA (methylenedioxymethamphetamine, also called ecstasy) significantly enhanced the treatment effects associated with manualized therapy for severe PTSD. *Mitchell JM et al. Nat Med. [PMID: 33972795]*
CHAPTER 28: LIPID DISORDERS		
Treatment of High LDL Cholesterol	1247	• The FDA approved the novel PCSK9 inhibitor inclisiran, which uses silencing RNA technology to reduce liver production of PCSK9 protein by approximately 80%. Twice-yearly dosing is novel for lipid-lowering therapy; inclisiran enables new delivery strategies, including in-clinic administration. *Raal FJ et al; ORION-9 Investigators. N Engl J Med. [PMID: 32197277]* *Ray KK et al; ORION-10 and ORION-11 Investigators. N Engl J Med. [PMID: 32187462]*
CHAPTER 29: NUTRITIONAL DISORDERS & OBESITY		
Obesity	1257	• Semaglutide, a GLP-1 receptor agonist, is FDA-approved for the treatment of obesity. *Wilding JPH et al. N Engl J Med. [PMID: 33567185]*
CHAPTER 30: COMMON PROBLEMS IN INFECTIOUS DISEASES & ANTIMICROBIAL THERAPY		
Infections in the Immunocompromised Patient	1276	• While the traditional approach was to continue antibiotics until resolution of neutropenia, current evidence supports earlier discontinuation of antibiotics in the neutropenic patient who becomes afebrile for 72 hours, if no signs or symptoms of infection persist.
CHAPTER 31: HIV INFECTION & AIDS		
HIV Infection & AIDS	1329	• In the ANCHOR study, which involved nearly 4500 individuals with anal high-grade squamous intraepithelial lesions (HGSIL), nine patients who were assigned to aggressive therapy (mostly office-based electrocautery) developed anal cancer compared with 21 of those in an active monitoring group, representing a 57% decrease in relative risk over the median 25.8-month follow-up period. This pivotal study will change care toward more aggressive screening for HGSIL and treatment to prevent progression to anal cancer. *Palefsky J et al. CROI 2022 (special session).*
	1332	• Cabotegravir was FDA-approved for use as preexposure prophylaxis as an injectable medication, every 8 weeks. This medication has been shown to be superior to oral tenofovir disoproxil fumarate/emtricitabine in preventing HIV infection among men who have sex with men, transgender women who have sex with men, and cisgender women in sub-Saharan Africa.
	1337	• Prophylaxis against *Mycobacterium avium* complex is no longer recommended in most individuals who are initiating antiretroviral therapy (ART), including in those with CD4+ counts less than 50 cells/mcL. The incidence of *M avium* complex infection is very low among those on ART.
	1338	• The TEMPRANO trial showed that individuals immediately initiating ART versus delaying treatment for CD4 count to fall below 500 cells/mcL had lower rates of severe illness.

*See chapter for further details and references.

Topic	Page Number	Key New Advances Affecting Clinical Practice*
CHAPTER 32: VIRAL & RICKETTSIAL INFECTIONS		
Ebola Viral Disease	1390	• The World Health Organization recommends automated or semi-automated nucleic acid tests (NATs) of EDTA-anticoagulated whole blood from symptomatic patients for routine diagnostic management, and rapid antigen detection tests in areas where NATs are not available. Oral fluid can be used for diagnostics when blood collection is not possible. *Choi MJ et al. MMWR Recomm Rep. [PMID: 33417593]*
Japanese Encephalitis	1382	• At least eight effective types of vaccine against Japanese encephalitis are available worldwide, including live attenuated and inactivated vaccines. *Kwak BO et al. Vaccine. [PMID: 33712352]*
Poliomyelitis	1375	• A novel oral polio vaccine type 2 (nOPV2) has been developed in response to the ongoing circulating vaccine-derived type 2 poliovirus outbreaks and has been shown to be safe and immunogenic in previously immunized adults. Studies have shown that nOPV2 is more genetically stable than the mOPV2 and therefore less prone to reverting to neurovirulence. The nOPV2 was recommended for initial use under the World Health Organization's Emergency Use Listing Procedure in November 2020. *Coster ID et al. Lancet. [PMID: 33308429]*
Severe Acute Respiratory Syndrome—COVID-19 (SARS-COV-2)	1401	• *CMDT* updates the ever-evolving knowledge of SARS-CoV-2 and the related disease online at www.accessmedicine.com
Tick-borne Encephalitis (TBE)	1383	• TicoVac (known as FSME-Immun in Europe) was FDA-approved. The vaccine is indicated for those residing and traveling to endemic areas (and the disease is now extending to higher altitudes with climate change). *Ličková M et al. Ticks Tick Borne Dis. [PMID: 32173297]*
CHAPTER 34: SPIROCHETAL INFECTIONS		
Lyme Disease (Lyme Borreliosis)	1493	• When assessing for CNS Lyme disease in an appropriate clinical syndrome, serum antibody testing is recommended over cerebrospinal fluid serology or PCR. • While serology is recommended to diagnose Lyme arthritis, PCR can be done on synovial fluid or tissue if needed to confirm the diagnosis and guide treatment. *Lantos PM et al. Clin Infect Dis. [PMID: 33417672]*
CHAPTER 35: PROTOZOAL & HELMINTHIC INFECTIONS		
African Trypanosomiasis (Sleeping Sickness)	1497	• Fexinidazole is recommended by the World Health Organization as first-line therapy and is FDA-approved for treatment of early and advanced (CNS) West African disease. *Hidalgo J et al. Cureus. [PMID: 34513456]*
Leishmaniasis	1501	• Alternative therapies increasingly used to treat cutaneous leishmaniasis are miltefosine, which benefits from oral dosing and relatively little toxicity, and amphotericin B, which is widely available. *Machado PRL et al. Clin Infect Dis. [PMID: 32894278]*
Malaria	1507	• Artemisinin resistance is mediated by any of a series of mutations in the *Plasmodium falciparum* kelch (K13) gene; of great concern, these same mutations and evidence for delayed clearance after treatment with artemisinins were reported in East Africa in 2021. *Balikagala B et al. N Engl J Med. [PMID: 34551228]*
CHAPTER 36: MYCOTIC INFECTIONS		
Candidiasis	1535	• Oral ibrexafungerp, a highly bioavailable glucan synthase inhibitor, may be used to treat vulvovaginal candidiasis from any disease-causing *Candida* strains, including azole-resistant pathogens. *Gold JAW et al. Clin Infect Dis. [PMID: 34079987]*

*See chapter for further details and references.

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Topic	Page Number	Key New Advances Affecting Clinical Practice*
CHAPTER 38: POISONING		
Marijuana & Synthetic Cannabinoids	1585	• Cannabidiol (CBD) is a constituent of Cannabis that does not produce THC-like intoxication. CBD extracts are available over the counter and via the internet for a variety of proposed effects (anti-inflammatory, antioxidant, anxiolysis) and by prescription for some pediatric seizure disorders. Overdoses are typically not dangerous. *Alves VL et al. Crit Rev Toxicol. [PMID: 32530350]*
Theophylline & Caffeine	1592	• Hemodialysis has been used in patients with caffeine overdose. • Extracorporeal membrane oxygenation has been used successfully in hemodynamic collapse after caffeine overdose. *Ou HC et al. Am J Emerg Med. [PMID: 34922795]* *Yasuda S et al. Acute Med Surg. [PMID: 33532077]*
CHAPTER 39: CANCER		
Bladder Cancer	1644	• Pembrolizumab is FDA-approved for patients with high-risk, non–muscle invasive bladder cancers who have failed intravesical bacillus Calmette–Guérin therapy. Nivolumab has also been approved in the adjuvant setting after radical cystectomy or nephroureterectomy for urothelial carcinoma at high risk for recurrence. • The fibroblast growth factor receptor inhibitor erdafitinib is approved after initial therapy for patients with progressive metastatic urothelial carcinoma whose tumors harbor these mutations with expected response rates of up to 40%. • Enfortumab vedotin is the first antibody-drug conjugate approved for advanced and metastatic urothelial carcinoma. The antibody targets Nectin-4 and demonstrates a 44% response rate (including 12% complete response) in patients who have progressed after multiple other lines of therapy. *Bajorin DF et al. N Engl J Med. [PMID: 34077643]* *Balar AV et al. Lancet Oncol. [PMID: 34051177]* *Rosenberg JE at al. J Clin Oncol. [PMID: 31356140]*
Bronchogenic Carcinoma	1606–1607	• The FDA approved sotorasib (AMG 510) for the treatment of *KRAS* G12C mutated lung cancers after progression on first-line treatment. • Atezolizumab (PD-L1 inhibitor) can be given for 1 year post–adjuvant chemotherapy for resected stage II to IIIA NSCLC, based on a phase 3 trial showing improvement in disease-free survival compared with adjuvant chemotherapy without atezolizumab. For stage III NSCLCs, a phase 3 trial has shown improved survival outcomes by adding durvalumab (PD-L1 inhibitor) as consolidation therapy post–definitive chemoradiation. • Five-year follow-up data for patients with 50% or greater PD-L1 expression show that patients who received pembrolizumab versus chemotherapy alone had improved median overall survival of 26 months versus 13 months. *Skoulidis F et al. N Engl J Med. [PMID: 34096690]* *Reck M et al. J Clin Oncol. [PMID: 33872070]* *Felip E et al. Lancet. [PMID: 34555333]*
Colorectal Cancer (CRC)	1630	• For the 50% of patients with metastatic CRC who have *KRAS/NRAS/BRAF* wild-type tumors, cetuximab and panitumumab (monoclonal antibodies to the epithelial growth factor receptor), in combination with chemotherapy, can extend median survival by 2 to 4 months compared with chemotherapy alone. For the 5% to 10% with BRAF V600E sequence variations, targeted combination therapy with BRAF and EGFR inhibitors extend overall survival to 9.3 months, compared with 5.9 months for those receiving standard chemotherapy.
	1633	• In four randomized clinical trials (n = 458,002), intention to screen with 1- or 2-time flexible sigmoidoscopy versus no screening was associated with a significant decrease in CRC–specific mortality. *National Comprehensive Cancer Network.* *https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf* *National Comprehensive Cancer Network.* *https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf* *Shaukat A et al. Am J Gastroenterol. [PMID: 33657038]*

*See chapter for further details and references.

Topic	Page Number	Key New Advances Affecting Clinical Practice*
Esophageal Cancer	1618	• For patients who complete neoadjuvant chemoradiation and undergo a complete resection but are found to have residual cancer in the resection specimen, a year of adjuvant immunotherapy with nivolumab is recommended. *Ahmed O et al. Clin Gastroenterol Hepatol. [PMID: 33813072]*
Gastric Adenocarcinoma	1621	• Triplet chemotherapy for resectable gastric cancer is recommended for patients who are fit but is associated with more toxicity than doublet chemotherapy.
	1622	• The development of immunotherapy represents a promising strategy in a selected patients with locally advanced and metastatic gastric cancer. Testing for microsatellite instability-high (MSI-H), mismatch repair deficiency (dMMR), PD-1, and PD-L1 is recommended in advanced disease to identify tumors that may respond to immunotherapy. *ASGE Standards of Practice Committee; Jue TL et al. Gastrointest Endosc. [PMID: 33168194]* *de Steur WO et al; CRITICS investigators. Ann Oncol. [PMID: 33227408]* *Kawazoe A et al. Jpn J Clin Oncol. [PMID: 33241322]* *Ng SP et al. Ann Surg Oncol. [PMID: 33689079]*
Malignancies of the Small Intestine	1625	• For advanced/unresectable disease, first-line doublet chemotherapy is standard. Two trials suggest value from adding bevacizumab to chemotherapy. Pembrolizumab is an accepted treatment modality for mismatch repair-deficient tumors. *National Comprehensive Cancer Network.* *https://www.nccn.org/professionals/physician_gls/pdf/small_bowel.pdf*
Prostate Cancer	1635	• Multiparametric MRI (mpMRI) has emerged as the imaging study of choice for localized prostate cancer detection and characterization. Suspicious prostatic lesions may then be sampled via MRI-guided needle biopsy or via MR Fusion (in which prostate MRI images are fused in real-time with images from an ultrasound-guided needle biopsy). Such an approach may improve discovery of potentially life-threatening disease while limiting over-detection of indolent prostate cancer or unnecessary prostate biopsies. *Kovac E et al. JAMA Netw Open. [PMID: 31940039]*
	1637	• NCCN guidelines recommend considering germline genetic testing in men presenting with localized high-risk, regionally advanced, or metastatic disease. Commercially available cancer tissue RNA-based assays are available for further risk assessment after prostate cancer diagnosis; these may help determine the need for and timing of prostate cancer treatment as well as treatment intensity. *Kovac E et al. JAMA Netw Open. [PMID: 31940039]*
	1637	• A secondary data analysis from the Prostate, Lung, Colorectal, and Ovarian trial demonstrated that baseline PSA for younger men in their 50s can predict long-term risk of prostate cancer and can be used to tailor PSA screening intervals. *Kovac E et al. JAMA Netw Open. [PMID: 31940039]*
	1638	• Active surveillance is now the preferred initial treatment recommendation for men with well-differentiated prostate cancer and low-risk clinical features. *Kovac E et al. JAMA Netw Open. [PMID: 31940039]*
	1641	• Results from the PEACE-1 trial demonstrate that a three-drug regimen, with androgen deprivation therapy, docetaxel and abiraterone acetate used together, provides the best survival outcome for men with hormone-naïve metastatic cancer. With this regimen, the median survival for men with de novo metastatic prostate cancer is now expected to be 5 years. *Kovac E et al. JAMA Netw Open. [PMID: 31940039]*
	1641	• Poly(ADP-ribose) polymerase (PARP) inhibitors represent a novel class of anticancer agents with some activity against prostate cancer, particularly those harboring mutations in genes important for homologous recombination such as *BRCA1*, *BRCA2*, and *ATM*. There are two FDA-approved PARP inhibitors available for men with metastatic castrate-resistant prostate cancer with these genetic alterations. *Kovac E et al. JAMA Netw Open. [PMID: 31940039]*

*See chapter for further details and references.

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Topic	Page Number	Key New Advances Affecting Clinical Practice*
Renal Cell Carcinoma	1646	• For patients with von Hippel-Lindau disease and renal cell carcinoma, belzutifan, a HIF2a inhibitor, leads to dramatic size reductions in both renal and non-renal neoplasms and offers a new treatment option. • Pembrolizumab is FDA-approved for adjuvant treatment after surgical resection of renal cell carcinoma in patients at high risk for disease recurrence. • The SURTIME randomized trial compared immediate versus deferred cytoreductive nephrectomy in patients with metastatic renal cell carcinoma treated with sunitinib and showed an overall survival advantage with the deferred approach. This may serve to identify patients who respond the best to systemic therapy prior to undergoing removal of the primary tumor. *Bex A et al. JAMA Oncol. [PMID: 30543350]* *Jonasch E et al. N Engl J Med. [PMID: 34818478]* *Rini BI et al; KEYNOTE-426 Investigators. N Engl J Med. [PMID: 30779529]*
Toxicity & Dose Modification of Chemotherapeutic Agents	1657	• The main toxicities of immune checkpoint inhibitors involve immune-related adverse events which occur via the same mechanisms as their antitumor effects (ie, self-reactive T-cells escaping central tolerance). The combination of PD-1 or PD-L1 inhibitors with CTLA-4 inhibitors results in higher rates of grade 3 or higher and all grades of immune-related adverse events. *Brahmer JR et al. J Immunother Cancer. [PMID: 34172516]*
CHAPTER 41: ORTHOPEDIC DISORDERS & SPORTS MEDICINE		
Dupuytren Contracture	1691	• Some evidence suggests superior clinical outcomes of percutaneous needle aponeurotomy for Dupuytren Contracture compared with collagenase *Clostridium histolyticum* (CCH) injections and a higher minor complication rate with CCH. *Hirase T et al. J Hand Microsurg. [PMID: 34511831]*
Low Back Pain	1685	• Heat treatments have shown to have short-term benefits for acute low back pain. • There is good evidence that spinal manipulation and acupuncture provide short-term improvement compared with usual care alone. • Intra-articular steroid injections and cooled radiofrequency ablation of the sacral lateral branch nerves and dorsal ramus of L5 can be considered for patients with persistent sacroiliac joint pain. There is fair evidence that thermal radiofrequency ablation of the facet joints improves pain for at least 6 months. *Kreiner DS et al. Spine J. [PMID: 32333996]*
CHAPTER 42: SEXUAL, GENDER, & MINORITY HEALTH		
Health Care for Lesbian & Bisexual Women	1718	• One study of 150 lesbian, bisexual, and queer women offered preliminary evidence that social support, resilience, and self-esteem help foster body appreciation, which might be protective against mental health concerns and disordered eating.
	1714	• A report demonstrated significantly better reproductive outcomes after reciprocal in vitro fertilization (IVF), with a clinical pregnancy rate of 60% compared with 40% after autologous IVF, and live birth rate of 57.1% in reciprocal IVF versus 29.8% in autologous IVF. However, both partners of the couple need to be willing to participate in reciprocal IVF. *Burnette CB et al. Health Equity. [PMID 31289784]* *Núñez A et al. LGBT Health. [PMID: 34061679]*

*See chapter for further details and references.

Disease Prevention & Health Promotion

1

Michael Pignone, MD, MPH[1]
René Salazar, MD

GENERAL APPROACH TO THE PATIENT

The medical interview serves several functions. It is used to collect information to assist in diagnosis (the "history" of the present illness), to understand patient values, to assess and communicate prognosis, to establish a therapeutic relationship, and to reach agreement with the patient about further diagnostic procedures and therapeutic options. It also serves as an opportunity to influence patient behavior, such as in motivational discussions about smoking cessation or medication adherence. Interviewing techniques that avoid domination by the clinician increase patient involvement in care and patient satisfaction. Effective clinician-patient communication and increased patient involvement can improve health outcomes.

Patient Adherence

For many illnesses, successful prevention and treatment depends on difficult fundamental behavioral changes, including altering diet, taking up exercise, giving up smoking, cutting down drinking, wearing masks to prevent infection, and adhering to medication regimens that are often complex. Adherence is a problem in every practice; up to 50% of patients fail to achieve full adherence, and one-third never take their medicines. Many patients with medical problems, even those with access to care, do not seek appropriate care or may drop out of care prematurely. Adherence rates for short-term, self-administered therapies are higher than for long-term therapies and are inversely correlated with the number of interventions, their complexity and cost, and the patient's perception of overmedication.

As an example, in HIV-infected patients, adherence to antiretroviral therapy is a crucial determinant of treatment success. Studies have unequivocally demonstrated a close relationship between patient adherence and plasma HIV RNA levels, CD4 cell counts, and mortality. Adherence levels of more than 95% are needed to maintain virologic suppression. However, studies show that 40% of patients are less than 90% adherent and that adherence tends to decrease over time.

Patient reasons for suboptimal adherence include simple forgetfulness, being away from home, being busy, and changing daily routine. Other reasons include psychiatric disorders (depression or substance misuse), uncertainty about the effectiveness of treatment, lack of knowledge about the consequences of poor adherence, regimen complexity, and treatment side effects. The rising costs of medications, including generic drugs, and the increase in patient cost-sharing burden, have made adherence even more difficult, particularly for those with lower incomes.

Patients seem better able to take prescribed medications than to adhere to recommendations to change their diet, exercise habits, or alcohol intake or to perform various self-care activities (such as monitoring blood glucose levels at home). For short-term regimens, adherence to medications can be improved by giving clear instructions. Writing out advice to patients, including changes in medication, may be helpful. Because low functional health literacy is common (almost half of English-speaking US patients are unable to read and understand standard health education materials), other forms of communication—such as illustrated simple text, videotapes, or oral instructions—may be more effective. For non–English-speaking patients, clinicians and health care delivery systems can work to provide culturally and linguistically appropriate health services.

To help improve adherence to long-term regimens, clinicians can work with patients to reach agreement on the goals for therapy, provide information about the regimen, ensure understanding by using the "teach-back" method, counsel about the importance of adherence and how to organize medication-taking, reinforce self-monitoring, provide more convenient care, prescribe a simple dosage regimen for all medications (preferably one or two doses daily), suggest ways to help in remembering to take doses (time of day, mealtime, alarms) and to keep appointments, prescribe lower-cost generic medications when available, and provide ways to simplify dosing (medication boxes). Single-unit doses supplied in foil wrappers can increase adherence but should be avoided for patients who have difficulty opening them. Medication boxes with

[1]Dr. Pignone is a former member of the US Preventive Services Task Force (USPSTF). The views expressed in this chapter are his and Dr. Salazar's and not necessarily those of the USPSTF.

compartments (eg, Medisets) that are filled weekly are useful. Microelectronic devices can provide feedback to show patients whether they have taken doses as scheduled or to notify patients within a day if doses are skipped. Reminders, including cell phone text messages, are another effective means of encouraging adherence. The clinician can also enlist social support from family and friends, recruit an adherence monitor, provide a more convenient care environment, and provide rewards and recognition for the patient's efforts to follow the regimen. Collaborative programs in which pharmacists help ensure adherence are also effective. Motivational interviewing techniques can be helpful when patients are ambivalent about their therapy.

Adherence is also improved when a trusting doctor-patient relationship has been established and when patients actively participate in their care. Clinicians can improve patient adherence by inquiring specifically about the behaviors in question. When asked, many patients admit to incomplete adherence with medication regimens, with advice about giving up cigarettes, or with engaging only in "safer sex" practices. Although difficult, sufficient time must be made available for communication of health messages.

Medication adherence can be assessed generally with a single question: "In the past month, how often did you take your medications as the doctor prescribed?" Other ways of assessing medication adherence include pill counts and refill records; monitoring serum, urine, or saliva levels of drugs or metabolites; watching for appointment nonattendance and treatment nonresponse; and assessing predictable drug effects, such as weight changes with diuretics or bradycardia from beta-blockers. In some conditions, even partial adherence, as with drug treatment of hypertension and diabetes mellitus, improves outcomes compared with nonadherence; in other cases, such as HIV antiretroviral therapy or tuberculosis treatment, partial adherence may be worse than complete nonadherence.

Guiding Principles of Care

Ethical decisions are often called for in medical practice, at both the "micro" level of the individual patient-clinician relationship and at the "macro" level of allocation of resources or the adoption of infection-reducing public health interventions. Ethical principles that guide the successful approach to diagnosis and treatment are honesty, beneficence, justice, avoidance of conflict of interest, and the pledge to do no harm. Increasingly, Western medicine involves patients in important decisions about medical care, eg, which colorectal screening test to obtain or which modality of therapy for breast cancer or how far to proceed with treatment of patients who have terminal illnesses (see Chapter 5).

The clinician's role does not end with diagnosis and treatment. The importance of the empathic clinician in helping patients and their families bear the burden of serious illness and death cannot be overemphasized. "To cure sometimes, to relieve often, and to comfort always" is a French saying as apt today as it was five centuries ago—as is Francis Peabody's admonition: "The secret of the care of the patient is in caring for the patient." Training to improve mindfulness and enhance patient-centered communication increases patient satisfaction and may also improve clinician satisfaction.

Daliri S et al. Medication-related interventions delivered both in hospital and following discharge: a systematic review and meta-analysis. BMJ Qual Saf. 2021;30:146. [PMID: 32434936]
Foley L et al. Prevalence and predictors of medication non-adherence among people living with multimorbidity: a systematic review and meta-analysis. BMJ Open. 2021;11:e044987. [PMID: 34475141]
Peh KQE et al. An adaptable framework for factors contributing to medication adherence: results from a systematic review of 102 conceptual frameworks. J Gen Intern Med. 2021;36:2784. [PMID: 33660211]

HEALTH MAINTENANCE & DISEASE PREVENTION

Preventive medicine can be categorized as primary, secondary, or tertiary. Primary prevention aims to remove or reduce disease risk factors (eg, immunization, giving up or not starting smoking). Secondary prevention techniques promote early detection of disease or precursor states (eg, routine cervical Papanicolaou screening to detect carcinoma or dysplasia of the cervix). Tertiary prevention measures are aimed at limiting the impact of established disease (eg, partial mastectomy and radiation therapy to remove and control localized breast cancer).

Tables 1–1 and 1–2 give leading causes of death in the United States for 2020 and recent estimates of deaths from preventable causes from 2019. The 2020 data demonstrate the large impact of COVID-19 on mortality and continue to show increased mortality rates, generally driven by the effects of COVID-19 as well as increases in deaths from

Table 1–1. Leading causes of death in the United States, 2020.

Category	Estimate
All causes	**3,358,814**
1. Diseases of the heart	690,882
2. Malignant neoplasms	598,932
3. COVID-19	345,323
4. Unintentional injuries	192,176
5. Cerebrovascular diseases	159,050
6. Chronic lower respiratory diseases	151,637
7. Alzheimer disease	133,382
8. Diabetes mellitus	101,106
9. Influenza and pneumonia	53,495
10. Nephritis, nephrotic syndrome, and nephrosis	52,260
11. Intentional self-harm (suicide)	44,834

Data from National Center for Health Statistics, 2021.

Table 1–2. Leading preventable causes of death in the United States, 2019.

Category	Estimate
Tobacco	546,401
High blood pressure	495,201
High fasting plasma glucose	439,212
Dietary risks	418,350
High BMI	392,352
High LDL cholesterol	226,343
Impaired kidney function	214,740
Alcohol use	136,866
Non-optimal temperature	126,623
Drug use	104,141

Data from the US Burden of Disease Collaborators, 2021.

heart disease, unintentional injuries (including overdoses), and Alzheimer disease.

Many effective preventive services are underutilized, and few adults receive all of the most strongly recommended services. Several methods, including the use of provider or patient reminder systems (including interactive patient health records), reorganization of care environments, and possibly provision of financial incentives to clinicians (though this remains controversial), can increase utilization of preventive services, but such methods have not been widely adopted.

Ahmad FB et al. The leading causes of death in the US for 2020. JAMA. 2021;325:1829. [PMID: 33787821]
Levine DM et al. Quality and experience of outpatient care in the United States for adults with or without primary care. JAMA Intern Med. 2019;179:363. [PMID: 30688977]
US Burden of Disease Collaborators. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. JAMA. 2018;319:1444. [PMID: 29634829]
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PREVENTION OF INFECTIOUS DISEASES

Much of the historic decline in the incidence and fatality rates of infectious diseases is attributable to public health measures—especially immunization, improved sanitation, nonpharmacologic interventions (eg, mask-wearing to prevent respiratory-transmissible conditions), and better nutrition. This observation has been reinforced by the experience during the global COVID-19 pandemic.

Immunization remains the best means of preventing many infectious diseases. Recommended immunization schedules for children and adolescents can be found online at http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html, and the schedule for adults is at http://www.cdc.gov/vaccines/schedules/hcp/adult.html (see also Chapter 30 and Chapter 32). In addition to the severe toll in morbidity and mortality from COVID-19, substantial morbidity and mortality continues to occur from vaccine-preventable diseases, such as hepatitis A, hepatitis B, influenza, and pneumococcal infections. The high incidence and mortality rates from COVID-19 and other recent outbreaks of vaccine-preventable diseases in the United States highlight the need to understand the association of vaccine hesistancy or refusal and disease epidemiology and methods for overcoming it.

The Advisory Committee on Immunization Practices recommendations for the following vaccines appears in Table 1–3: influenza; measles, mumps, and rubella; 23-valent pneumococcal polysaccharide vaccine; tetanus, diphtheria, and acellular pertussis; hepatitis B; and HPV.

Persons traveling to countries where infections are endemic should take the precautions described in Chapter 30 and at https://wwwnc.cdc.gov/travel/destinations/list. Immunization registries—confidential, population-based, computerized information systems that collect vaccination data about all residents of a geographic area—can be used to increase and sustain high vaccination coverage.

Globally, **COVID-19** has resulted in over 5 million deaths. COVID-19 is caused by SARS-CoV-2. The impact on frontline workers, including health care workers, has been substantial, and the pandemic has revealed profound inequities in health and health care. In the United States, the COVID-19 mortality rates are higher in Black, Latinx, and Native American people compared to White people. Three COVID-19 vaccines are currently approved or authorized in the United States (Pfizer-BioNTech/Comirnaty, Moderna, and Janssen [Johnson & Johnson]). Currently, the CDC recommends everyone ages 5 and older get a COVID-19 vaccine to help protect against COVID-19 (see Chapter 32). Recent guidance has recommended third-dose boosters to be administered 6 months after primary series completion for individuals receiving Pfizer and Moderna mRNA-vaccines and 2 months after those receiving the Janssen adenovirus vector vaccine.

The USPSTF recommends behavioral counseling for adolescents and adults who are sexually active and at increased risk for **sexually transmitted infections.** Sexually active women aged 24 years or younger and older women who are at increased risk for infection should be screened for chlamydia and gonorrhea. Screening HIV-positive men or men who have sex with men for syphilis every 3 months is associated with improved syphilis detection.

The CDC recommends universal HIV screening of all patients aged 13–64, and the USPSTF recommends that clinicians screen adolescents and adults aged 15–65 years. Clinicians should integrate biomedical and behavioral approaches for HIV prevention. In addition to reducing sexual transmission of HIV, initiation of antiretroviral therapy reduces the risk for AIDS-defining events and death among patients with less immunologically advanced disease.

Daily **preexposure prophylaxis (PrEP)** with the fixed-dose combination of tenofovir disoproxil 300 mg and emtricitabine 200 mg (Truvada) should be considered for people who are HIV-negative but at substantial risk for HIV infection. Studies of men who have sex with men suggest that PrEP is very effective in reducing the risk of

Table 1–3. Advisory Committee on Immunization Practices vaccine recommendations, 2021.

Vaccine	Recommendation	Comment
Influenza	Routine vaccination for all persons aged 6 months and older, including all adults An alternative high-dose inactivated vaccine is available for adults aged 65 years and older	When vaccine supply is limited, certain groups should be given priority, such as adults aged 50 years and older, individuals with chronic illness or immunosuppression, and pregnant women
MMR	Two doses for adults at high risk for exposure and transmission (eg, college students, health care workers); otherwise, one dose for adults aged 18 years and older	Physician documentation of disease is not acceptable evidence of MMR immunity
PPSV23	Adults aged 65 and older If PPSV23 was administered prior to age 65 years, administer one dose PPSV23 at least 5 years after previous dose A shared clinical decision-making approach is recommended for use of PCV13 in average-risk individuals aged 65 and older	
Tdap	Routine use of a single dose of for adults aged 19–64 years	Replaces the next booster dose of Td
Hepatitis B	Three-dose series is recommended for all children aged 0–18 years and high-risk individuals (ie, health care workers, injection drug users, people with ESKD) Recommended for diabetic patients aged 19–59 years Should be considered in diabetic persons age 60 and older	Prevents chronic hepatitis B and cirrhosis and their predispositions to HCC
HPV VLP	Routine HPV vaccination for children and adults aged 9–26 years Shared decision-making is recommended for some individuals between 27 and 45 years of age (vaccine is not licensed for adults older than 45 years)	Prevents persistent HPV infections effectively and thus may impact the rate of CIN II–II

CIN, cervical intraepithelial neoplasia; HCC, hepatocellular carcinoma; HPV VLP, human papillomavirus virus-like particle vaccine; MMR, measles, mumps, and rubella vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; Td, tetanus and diphtheria toxoids vaccine; Tdap, tetanus, diphtheria, and five-component acellular pertussis vaccine.

contracting HIV. Patients taking PrEP should be encouraged to use other prevention strategies, such as consistent condom use to maximally reduce their risk. **Postexposure prophylaxis (PEP)** with combinations of antiretroviral drugs is widely used after occupational and nonoccupational contact and may reduce the risk of transmission by approximately 80%. PEP should be initiated within 72 hours of exposure.

Herpes zoster, caused by reactivation from previous varicella zoster virus infection, affects many older adults and people with immune system dysfunction. The ACIP recommends the herpes zoster subunit vaccine (HZ/su; Shingrix) be used for the prevention of herpes zoster and related complications in immunocompetent adults age 50 and older and in individuals who previously received Zostavax.

Centers for Disease Control and Prevention (CDC). COVID-19, 2021. https://www.cdc.gov/coronavirus/2019-ncov/index.html
Centers for Disease Control and Prevention (CDC). About COVID-19 vaccines (updated January 21, 2022). https://www.cdc.gov/coronavirus/2019-ncov/vaccines/about-vaccines/index.html
Centers for Disease Control and Prevention (CDC). Pneumococcal vaccination. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html
Centers for Disease Control and Prevention (CDC). Recommended adult immunization schedule for ages 19 years or older, United States, 2020. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html
Chou R et al. Epidemiology of and risk factors for coronavirus infection in health care workers: a living rapid review. Ann Intern Med. 2020;173:120. [PMID: 32369541]

PREVENTION OF CARDIOVASCULAR DISEASE

CVDs, including CHD and stroke, represent two of the most important causes of morbidity and mortality in developed countries. Several risk factors increase the risk for coronary disease and stroke. These risk factors can be divided into those that are modifiable (eg, lipid disorders, hypertension, cigarette smoking) and those that are not (eg, age, sex, family history of early coronary disease). Impressive declines in age-specific mortality rates from heart disease and stroke have been achieved in all age groups in North America from 1980 to 2015, in large part through improvement of modifiable risk factors: reductions in cigarette smoking, improvements in lipid levels, and more aggressive detection and treatment of hypertension. However, the past several years have seen a disturbing increase in cardiovascular deaths in the United States and leveling off of the reduction in cardiovascular mortality rates. This section considers the role of screening for cardiovascular risk and the use of effective therapies to reduce such risk. Key recommendations for cardiovascular prevention are shown in Table 1–4. Guidelines encourage regular assessment of global cardiovascular risk in adults 40–79 years of age without known CVD, using standard

Table 1–4. Expert recommendations for cardiovascular risk prevention methods: USPSTF.[1]

Prevention Method	Recommendation/[Year Issued]
Screening for AAA	Recommends one-time screening for AAA by ultrasonography in men aged 65–75 years who have ever smoked. (B) Selectively offer screening for AAA in men aged 65–75 years who have never smoked. (C) Current evidence is insufficient to assess the balance of benefits and harms of screening for AAA in women aged 65–75 years who have ever smoked or have a family history of AAA. (I) Recommends against routine screening for AAA in women who have never smoked and have no family history of AAA. (D) [2019]
Aspirin use	Recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50–59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. (B) The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60–69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin. (C) The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years or older than age 70. (I) [2016]
Blood pressure screening	Recommends screening for hypertension in adults 18 years or older with office blood pressure measurement. Recommends obtaining blood pressure measurements outside of the clinical setting for diagnostic confirmation before starting treatment. (A) [2021]
Serum lipid screening and use of statins for prevention	Recommends that adults without a history of CVD use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: (1) they are aged 40–75 years; (2) they have one or more CVD risk factors (ie, dyslipidemia, diabetes mellitus, hypertension, or smoking); and (3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater. Identification of dyslipidemia and calculation of 10-year CVD event risk requires universal lipids screening in adults aged 40–75 years. See the "Clinical Considerations" section of the USPSTF recommendations[1] for more information on lipids screening and the assessment of cardiovascular risk. (B) Concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating statin use for the primary prevention of CVD events and mortality in adults aged 76 years and older without a history of heart attack or stroke. (I) [2016]
Counseling about healthful diet and physical activity for CVD prevention	Recommends offering or referring adults with cardiovascular disease risk factors to behavioral counseling interventions to promote a healthy diet and physical activity. (B) [2020] Recommends that primary care professionals individualize the decision to offer or refer adults without obesity who do not have hypertension, dyslipidemia, abnormal blood glucose levels, or diabetes to behavioral counseling to promote a healthful diet and physical activity. (C) [2017]
Screening for diabetes mellitus	The USPSTF recommends screening for prediabetes and type 2 diabetes in adults aged 35–70 years who have overweight or obesity. Clinicians should offer or refer patients with prediabetes to effective preventive interventions. (B) [2021]
Screening for smoking and counseling to promote cessation	Recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide those who use tobacco behavioral interventions, and prescribe US FDA–approved pharmacotherapy to nonpregnant adults. (A) [2021]

USPSTF recommendations available at http://www.uspreventiveservicestaskforce.org/BrowseRec/Index/browse-recommendations.
Recommendation A: The USPSTF strongly recommends that clinicians routinely provide the service to eligible patients. (The USPSTF found good evidence that the service improves important health outcomes and concludes that benefits substantially outweigh harms.)
Recommendation B: The USPSTF recommends that clinicians routinely provide the service to eligible patients. (The USPSTF found at least fair evidence that the service improves important health outcomes and concludes that benefits substantially outweigh harms.)
Recommendation C: The USPSTF makes no recommendation for or against routine provision of the service.
Recommendation D: The USPSTF recommends against routinely providing the service to asymptomatic patients. (The USPSTF found at least fair evidence that the service is ineffective or that harms outweigh benefits.)
Recommendation I: The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing the service.

cardiovascular risk factors. The role of nontraditional risk factors for improving risk estimation remains unclear.

Cho L et al. Summary of updated recommendations for primary prevention of cardiovascular disease in women: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75:2602. [PMID: 32439010]
Roth GA et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol. 2020;76:2982. [PMID: 33309175]

Abdominal Aortic Aneurysm

One-time screening for AAA by ultrasonography is recommended by the USPSTF (B recommendation) in men aged 65–75 years who have ever smoked. One-time screening for AAA is associated with a relative reduction in odds of AAA-related mortality over 12–15 years (OR, 0.65 [95% CI 0.57–0.74]) and a similar reduction in AAA-related ruptures (OR, 0.62 [95% CI 0.55–0.70]). Women who have never smoked and who have no family history of AAA do not appear to benefit from such screening (D recommendation); the current evidence for women who have ever smoked or who have a family history of AAA is insufficient to assess the balance of risks versus benefits (I recommendation) (Table 1–4).

Guirguis-Blake JM et al. Primary care screening for abdominal aortic aneurysm: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2019;322:2219. [PMID: 31821436]
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Cigarette Smoking

Cigarette smoking remains the most important cause of preventable morbidity and early mortality. In 2019, there were an estimated 7.69 million deaths in the world attributable to smoking and tobacco use (13.6% of all deaths worldwide); smoking is the second leading cause of disability-adjusted life-years lost overall and leading cause among men. Cigarettes are responsible for one in every five deaths in the United States, or over 480,000 deaths annually. Annual cost of smoking-related health care is approximately $130 billion in the United States, with another $150 billion in productivity losses. Fortunately, US smoking rates have been declining; in 2015, 15.1% of US adults were smokers, and by 2018, 13.7% were smokers. Global direct health care costs from smoking in 2012 were estimated at $422 billion, with total costs of over $1.4 trillion.

Over 1.3 million deaths worldwide are attributed to secondhand smoke in 2019.

Although tobacco use constitutes one of the most serious common medical problems, it is undertreated. Almost 40% of smokers attempt to quit each year, but only 4% are successful. Persons whose clinicians advise them to quit are 1.6 times as likely to attempt quitting. Over 70% of smokers see a physician each year, but only 20% of them receive any medical quitting advice or assistance.

Factors associated with successful cessation include having a rule against smoking in the home, being older, and having greater education. Several effective clinical interventions are available to promote smoking cessation, including counseling, pharmacotherapy, and combinations of the two.

Helpful counseling strategies are shown in Table 1–5. Additionally, a system should be implemented to identify smokers, and advice to quit should be tailored to the patient's level of readiness to change. All patients trying to quit should be offered pharmacotherapy (Table 1–6) except those with medical contraindications, women who are

Table 1–5. Inquiries to help in support of smoking cessation.

Component	Helpful Clinician Statements and Inquiries
Communicate your caring and concern	"I am concerned about the effects of smoking on your health… • and want you to know that I am willing to help you quit." • and so how do you feel about quitting?" • do you have any fears or ambivalent feelings about quitting?"
Encourage the patient to talk about the quitting process	"Tell me… • why do you want to quit smoking?" • when you tried quitting smoking in the past, what sort of difficulties did you encounter?" • were you able to succeed at all, even for a while?" • what concerns or worries do you have about quitting now?"
Provide basic information about smoking (eg, its addictive nature) and successful quitting (eg, nature and time course of withdrawal)	"Did you know that… • the nicotine in cigarette smoke is highly addictive?" • within a day of stopping, you will notice nicotine withdrawal symptoms, such as irritability and craving?" • after you quit, any smoking (even a single puff) makes it likely that you will fully relapse into smoking again?"
Encourage the patient to make a quit attempt	"I want you to reassure you that… • as your clinician, I believe you are going to be able to quit." • there are now available many effective smoking cessation treatments." • more than half the people who have *ever* smoked have now successfully quit."

Table 1–6. Medications for tobacco dependence and smoking cessation.

Drug	Some Formulations	Usual Adult Dosage[1,2]	Cost 30/days
Nicotine Replacement Therapies (NRTs)			
Nicotine transdermal patch[3] – generic (NicoDerm CQ)	7, 14, 21 mg/24-h patches	1 patch/day[4]	$51.40
Nicotine polacrilex gum[3] – generic (Nicorette gum)	2, 4 mg/pieces	8–24 pieces/day[4,5,6]	$63.12
Nicotine polacrilex lozenge[3,7] – generic (Nicorette lozenge)	2, 4 mg/lozenges	8–20 lozenges/day[4,5,8]	$66.24
Nicotine oral inhaler – Nicotrol	10 mg cartridges[9]	4–16 cartridges/day[4]	$578.66
Nicotine nasal spray – Nicotrol NS	200 sprays/10 mL bottles (0.5 mg/spray)	2 sprays 8–40×/day (max 10 sprays/h)[3]	$607.60 (4-bottle package)
Dopaminergic-Noradrenergic Reuptake Inhibitor			
Bupropion SR – generic	100, 150, 200 mg SR tablets[10]	150 mg orally once daily × 3 days, then 150 mg orally twice daily	$112.80
Nicotinic Receptor Partial Agonist			
Varenicline tartrate – Chantix	0.5, 1 mg tablets	0.5 mg orally once daily × 3 days, then 0.5 mg twice daily on days 4–7, then 1 mg twice daily	$603.41

SR, sustained-release.
[1]Dosage reductions may be needed for liver or kidney impairment.
[2]Patients should receive a minimum of 3–6 months of effective therapy. In general, the dosage of NRTs can be tapered at the end of treatment; bupropion SR and varenicline can usually be stopped without a gradual dosage reduction, but some clinicians recommend a taper.
[3]Available over the counter for persons ≥ 18 years old.
[4]See expanded table for dosage titration instructions, available at: medicalletter.org/TML-article-1576c.
[5]Avoid eating or drinking within 15 minutes of using a gum or lozenge.
[6]A second piece of gum can be used within 1 hour. Continuously chewing one piece after another is not recommended.
[7]Also available in a mini-lozenge.
[8]Maximum of 5 lozenges in 6 hours or 20 lozenges/day. Use of more than 1 lozenge at a time or continuously using one after another is not recommended.
[9]Each cartridge delivers 4 mg of nicotine.
[10]Only the generic 150-mg SR tablets are FDA-approved as a smoking cessation aid.
Reprinted with special permission from The Medical Letter on Drugs and Therapeutics, July 15, 2019; Vol. 61 (1576):106.
Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: IBM Micromedex® Red Book (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at https://www-micromedexsolutions-com.proxy.hsl.ucdenver.edu (cited: March, 11, 2022). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

pregnant or breast-feeding, and adolescents. Weight gain occurs in most patients (80%) following smoking cessation. Average weight gain is 2 kg, but for some (10–15%), major weight gain—over 13 kg—may occur. Planning for the possibility of weight gain, and means of mitigating it, may help with maintenance of cessation.

Several pharmacologic therapies shown to be effective in promoting cessation are summarized in Table 1–6. Nicotine replacement therapy doubles the chance of successful quitting. The nicotine patch, gum, and lozenges are available over the counter and nicotine nasal spray and inhalers by prescription. The sustained-release antidepressant drug bupropion (150–300 mg/day orally) is an effective smoking cessation agent and is associated with minimal weight gain, although seizures are a contraindication. It acts by boosting brain levels of dopamine and norepinephrine, mimicking the effect of nicotine. Varenicline, a partial nicotinic acetylcholine-receptor agonist, has been shown to improve cessation rates; however, its adverse effects, particularly its effects on mood, are not completely understood and warrant careful consideration. No single pharmacotherapy is clearly more effective than others, so patient preferences and data on adverse effects should be taken into account in selecting a treatment. Combination therapy is more effective than a single pharmacologic modality. The efficacy of e-cigarettes in smoking cessation has not been well evaluated, and some users may find them addictive. Recent reports of "vaping-related" lung disease should prompt additional caution in the use of unregulated nicotine delivery devices for smoking cessation (see Chapter 9).

Clinicians should not show disapproval of patients who fail to stop smoking or who are not ready to make a quit attempt. Thoughtful advice that emphasizes the benefits of cessation and recognizes common barriers to success can

increase motivation to quit and quit rates. An upcoming medical procedure or intercurrent illness or hospitalization may motivate even the most addicted smoker to quit.

Individualized or group counseling is very cost effective, even more so than treating hypertension. Smoking cessation counseling by telephone ("quitlines") and text messaging–based interventions have both proved effective. An additional strategy is to recommend that any smoking take place outdoors to limit the effects of passive smoke on housemates and coworkers. This can lead to smoking reduction and quitting.

Public policies, including higher cigarette taxes and more restrictive public smoking laws, have also been shown to encourage cessation, as have financial incentives directed to patients.

Anonymous. Drugs for smoking cessation. Med Lett Drugs Ther. 2019;61:105. [PMID: 31381546]
Black N et al. Behaviour change techniques associated with smoking cessation in intervention and comparator groups of randomized controlled trials: a systematic review and meta-regression. Addiction. 2020;115:2008. [PMID: 32196796]
Centers for Disease Control and Prevention (CDC). Current cigarette smoking among adults in the United States. 2020 December 10. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm
Hollands GJ et al. Interventions to increase adherence to medications for tobacco dependence. Cochrane Database Syst Rev. 2019;8:CD009164. [PMID: 31425618]
Tibuakuu M et al. National trends in cessation counseling, prescription medication use, and associated costs among US adult cigarette smokers. JAMA Netw Open. 2019;2:e194585. [PMID: 31125108]
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Lipid Disorders

Higher LDL cholesterol concentrations and lower HDL levels are associated with an increased risk of CHD (see Chapter 28). Measurement of total and HDL cholesterol levels can help assess the degree of CHD risk. The best age to start screening is controversial, as is its frequency. Cholesterol-lowering therapy reduces the relative risk of CHD events, with the degree of reduction proportional to the reduction in LDL cholesterol achieved, at least at initial LDL levels greater than 100 mg/dL. The absolute benefits of screening for—and treating—abnormal lipid levels depend on the presence and level of other cardiovascular risk factors, including hypertension, diabetes mellitus, smoking, age, and sex. If other risk factors are present, atherosclerotic CVD risk is higher and the potential benefits of therapy are greater. Patients with known CVD are at higher risk and have larger benefits from reduction in LDL cholesterol. The optimal risk threshold for initiating statins for primary prevention remains somewhat controversial, although most guidelines now suggest statin therapy when the 10-year atherosclerotic cardiovascular risk is greater than 10%. Use of a cardiovascular risk calculator can help inform decision making for primary prevention.

Evidence for the effectiveness of statin-type drugs is better than for the other classes of lipid-lowering agents or dietary changes specifically for improving lipid levels. Multiple large, randomized, placebo-controlled trials have demonstrated important reductions in total mortality, major coronary events, and strokes with lowering levels of LDL cholesterol by statin therapy for patients with known CVD. Statins also reduce cardiovascular events for patients with diabetes mellitus. For patients with no previous history of cardiovascular events or diabetes, meta-analyses have shown important reductions of cardiovascular events.

Newer antilipidemic monoclonal antibody agents (eg, evolocumab and alirocumab) lower LDL cholesterol by 50–60% by binding proprotein convertase subtilisin kexin type 9 (PCSK9), which decreases the degradation of LDL receptors. PCSK9 inhibitors also decrease Lp(a) levels. These newer agents are very expensive so are often used mainly in high-risk patients when statin therapy does not reduce the LDL cholesterol sufficiently at maximally tolerated doses or when patients are intolerant of statins. So far, few side effects have been reported with PCSK9 inhibitor use.

Guidelines for statin and PCSK9 therapy are discussed in Chapter 28.

Lloyd-Jones DM et al. Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: a special report from the American Heart Association and American College of Cardiology. Circulation. 2019;139:e1162. [PMID: 30423392]
Mortensen MB et al. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort. Lancet. 2020;396:1644. [PMID: 33186534]
Navarese EP et al. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. JAMA. 2018;319:1566. [PMID: 29677301]

Hypertension

According to the American Heart Association, over 133 million US adults have hypertension, of which approximately 83 million are eligible for pharmacologic treatment. Of these 83 million, hypertension is treated in only about 66% and well controlled in only about 30% (see Chapter 11). In every adult age group, higher values of systolic and diastolic blood pressure carry greater risks of stroke and heart failure. Systolic blood pressure is a better predictor of morbid events than diastolic blood pressure. Home monitoring is better correlated with target organ damage than clinic-based values. Clinicians can apply specific blood pressure criteria, such as those of the Joint National Committee or American Heart Association guidelines, along with consideration of the patient's cardiovascular risk and personal values, to decide at what levels treatment should be considered in individual cases.

Primary prevention of hypertension can be accomplished by strategies aimed at both the general population and special high-risk populations. The latter include persons with high-normal blood pressure or a family history of hypertension, Blacks, and individuals with various behavioral risk factors, such as physical inactivity; excessive consumption of salt, alcohol, or calories; and deficient

intake of potassium. Effective interventions for primary prevention of hypertension include reduced sodium and alcohol consumption, weight loss, and regular exercise. Potassium supplementation lowers blood pressure modestly, and a diet high in fresh fruits and vegetables and low in fat, red meats, and sugar-containing beverages also reduces blood pressure. Interventions of unproven efficacy include pill supplementation of potassium, calcium, magnesium, fish oil, or fiber; macronutrient alteration; and stress management.

Improved identification and treatment of hypertension has been a major cause of the decline in stroke deaths as well as the reduction in incidence of heart failure–related hospitalizations; more recently, stalled progress in control of hypertension has led to slowing of improvements in cardiovascular outcomes. Because hypertension is usually asymptomatic, screening is strongly recommended to identify patients for treatment. Elevated office readings should be confirmed with repeated measurements, ideally from ambulatory monitoring or home measurements. Despite strong recommendations in favor of screening and treatment, hypertension control remains suboptimal. An intervention that included both patient and provider education was more effective than provider education alone in achieving control of hypertension, suggesting the benefits of patient participation; another trial found that home monitoring combined with telephone-based nurse support was more effective than home monitoring alone for blood pressure control. Pharmacologic management of hypertension is discussed in Chapter 11.

Bundy JD et al. Comparison of the 2017 ACC/AHA Hypertension Guideline with earlier guidelines on estimated reductions in cardiovascular disease. Curr Hypertens Rep. 2019;21:76. [PMID: 31473837]
Centers for Disease Control and Prevention (CDC). Million Hearts 2022: estimated hypertension prevalence, treatment, and control among U.S. adults. https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html
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US Preventive Services Task Force. Screening for hypertension in adults: US preventive services task force reaffirmation recommendation statement. JAMA. 2021;325:1650. [PMID: 33904861]

Chemoprevention

Regular use of low-dose aspirin (81–325 mg) can reduce cardiovascular events but increases GI bleeding and hemorrhagic stroke. The potential benefits of aspirin may exceed the possible adverse effects among middle-aged adults who are at increased cardiovascular risk, which can be defined as a 10-year risk of greater than 10%, and who do not have an increased risk of bleeding. A newer trial in older healthy adults did not find clear benefit from aspirin for reduction of cardiovascular events and saw an increase in all-cause mortality with aspirin. Therefore, aspirin should not be routinely initiated in healthy adults over age 70.

NSAIDs may reduce the incidence of colorectal adenomas and polyps but may also increase heart disease and GI bleeding, and thus are not recommended for colon cancer prevention in average-risk patients.

Antioxidant vitamin (vitamin E, vitamin C, and beta-carotene) supplementation produced no significant reductions in the 5-year incidence of—or mortality from—vascular disease, cancer, or other major outcomes in high-risk individuals with CAD, other occlusive arterial disease, or diabetes mellitus.

Gaziano JM. Aspirin for primary prevention: clinical considerations in 2019. JAMA. 2019;321:253. [PMID: 30667488]
Huang WY et al. Frequency of intracranial hemorrhage with low-dose aspirin in individuals without symptomatic cardiovascular disease: a systematic review and meta-analysis. JAMA Neurol. 2019;76:906. [PMID: 31081871]
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Patrono C et al. Role of aspirin in primary prevention of cardiovascular disease. Nat Rev Cardiol. 2019;16:675. [PMID: 31243390]
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PREVENTION OF OSTEOPOROSIS

See Chapter 26.

Osteoporosis, characterized by low bone mineral density, is common and associated with an increased risk of fracture. The lifetime risk of an osteoporotic fracture is approximately 50% for women and 30% for men. Osteoporotic fractures can cause significant pain and disability. As such, research has focused on means of preventing osteoporosis and related fractures. Primary prevention strategies include calcium supplementation, vitamin D supplementation, and exercise programs. The effectiveness of calcium and vitamin D for fracture prevention remains controversial, particularly in noninstitutionalized individuals.

Screening for osteoporosis on the basis of low bone mineral density is recommended for women over age 65, based on indirect evidence that screening can identify women with low bone mineral density and that treatment of women with low bone density with bisphosphonates is effective in reducing fractures. However, real-world adherence to pharmacologic therapy for osteoporosis is low: one-third to one-half of patients do not take their medication as directed. Screening for osteoporosis is also recommended in younger women who are at increased risk. The effectiveness of screening in men has not been established. Concern has been raised that bisphosphonates may increase the risk of certain uncommon atypical types of femoral fractures and rare osteonecrosis of the jaw, making consideration of the benefits and risks of therapy important when considering osteoporosis screening.

US Preventive Services Task Force. Screening for osteoporosis to prevent fractures: US Preventive Services Task Force recommendation statement. JAMA. 2018;319:2521. [PMID: 29946735]

US Preventive Services Task Force. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: US Preventive Services Task Force recommendation statement. JAMA. 2018;319:1592. [PMID: 29677309]
Yedavally-Yellayi S et al. Update on osteoporosis. Prim Care. 2019;46:175. [PMID: 30704657]

PREVENTION OF PHYSICAL INACTIVITY

Lack of sufficient physical activity is the second most important contributor to preventable deaths, trailing only tobacco use. The US Department of Health and Human Services and the CDC recommend that adults (including older adults) engage in 150 minutes of moderate-intensity (such as brisk walking) or 75 minutes of vigorous-intensity (such as jogging or running) aerobic activity or an equivalent mix of moderate- and vigorous-intensity aerobic activity each week. In addition to activity recommendations, the CDC recommends activities to strengthen all major muscle groups (abdomen, arms, back, chest, hips, legs, and shoulders) at least twice a week.

Patients who engage in regular moderate to vigorous exercise have a lower risk of MI, stroke, hypertension, hyperlipidemia, type 2 diabetes mellitus, diverticular disease, and osteoporosis. Regular exercise may also have a positive effect on executive function in older adults.

In longitudinal cohort studies, individuals who report higher levels of leisure-time physical activity are less likely to gain weight. Conversely, individuals who are overweight are less likely to stay active. However, at least 60 minutes of daily moderate-intensity physical activity may be necessary to maximize weight loss and prevent significant weight regain. Moreover, adequate levels of physical activity appear to be important for the prevention of weight gain and the development of obesity.

Physical activity can be incorporated into any person's daily routine. The basic message should be the more the better, and anything is better than nothing.

When counseling patients, clinicians should advise patients about both the benefits and risks of exercise, prescribe an exercise program appropriate for each patient, and provide advice to help prevent injuries and cardiovascular complications.

Although primary care providers regularly ask patients about physical activity and advise them with verbal counseling, few providers provide written prescriptions or perform fitness assessments. Tailored interventions may potentially help increase physical activity in individuals. Exercise counseling with a prescription, eg, for walking at either a hard intensity or a moderate intensity with a high frequency, can produce significant long-term improvements in cardiorespiratory fitness. To be effective, exercise prescriptions must include recommendations on type, frequency, intensity, time, and progression of exercise and must follow disease-specific guidelines. Several factors influence physical activity behavior, including personal, social (eg, family and work), and environmental (eg, access to exercise facilities and well-lit parks) factors.

Chen FT et al. Effects of exercise training interventions on executive function in older adults: a systematic review and meta-analysis. Sports Med. 2020;50:1451. [PMID: 32447717]
Jeong SW et al. Mortality reduction with physical activity in patients with and without cardiovascular disease. Eur Heart J. 2019;40:3547. [PMID: 31504416]

PREVENTION OF OVERWEIGHT & OBESITY

Obesity is now a true epidemic and public health crisis that both clinicians and patients must face. Normal body weight is defined as a BMI of less than 25, overweight is defined as a BMI of 25.0–29.9, and obesity as a BMI greater than 30.

Risk assessment of the overweight and obese patient begins with determination of BMI, waist circumference for those with a BMI of 35 or less, presence of comorbid conditions, and a fasting blood glucose and lipid panel. Obesity is clearly associated with type 2 diabetes mellitus, hypertension, hyperlipidemia, cancer, osteoarthritis, cardiovascular disease, obstructive sleep apnea, and asthma.

Obesity is associated with a higher all-cause mortality rate. Data suggest an increase among those with grades 2 and 3 obesity (BMI more than 35); however, the impact on all-cause mortality among overweight (BMI 25–30) and grade 1 obesity (BMI 30–35) is questionable. Persons with a BMI of 40 or higher have death rates from cancers that are 52% higher for men and 62% higher for women than the rates in men and women of normal weight.

Prevention of overweight and obesity involves both increasing physical activity and dietary modification to reduce caloric intake. Adequate levels of physical activity appear to be important for the prevention of weight gain and the development of obesity. Physical activity programs consistent with public health recommendations may promote modest weight loss (~2 kg); however, the amount of weight loss for any one individual is highly variable.

Clinicians can help guide patients to develop personalized eating plans to reduce energy intake, particularly by recognizing the contributions of fat, concentrated carbohydrates, and large portion sizes (see Chapter 29). Patients typically underestimate caloric content, especially when consuming food away from home. Providing patients with caloric and nutritional information may help address the current obesity epidemic.

Commercial weight loss programs are effective in promoting weight loss and weight loss management. A randomized controlled trial of over 400 overweight or obese women demonstrated the effectiveness of a free prepared meal and incentivized structured weight loss program compared with usual care.

Weight loss strategies using dietary, physical activity, or behavioral interventions can produce significant improvements in weight among persons with prediabetes and a significant decrease in diabetes incidence. Lifestyle interventions including diet combined with physical activity are effective in achieving weight loss and reducing cardiometabolic risk factors among patients with severe obesity.

Bariatric surgical procedures, eg, adjustable gastric band, sleeve gastrectomy, and Roux-en-Y gastric bypass, are reserved for patients with morbid obesity whose BMI exceeds 40, or for less severely obese patients (with BMIs between 35 and 40) with high-risk comorbid conditions such as life-threatening cardiopulmonary problems or severe diabetes mellitus. In selected patients, surgery can produce substantial weight loss (10–159 kg) over 1–5 years, with rare but sometimes severe complications. Nutritional deficiencies are one complication of bariatric surgical procedures and close monitoring of a patient's metabolic and nutritional status is essential.

Finally, clinicians seem to share a general perception that almost no one succeeds in long-term maintenance of weight loss. However, research demonstrates that approximately 20% of overweight individuals are successful at long-term weight loss (defined as losing 10% or more of initial body weight and maintaining the loss for 1 year or longer).

Ryan DH et al. Guideline recommendations for obesity management. Med Clin North Am. 2018;102:49. [PMID: 29156187]
Wadden TA et al; STEP 3 Investigators. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. JAMA. 2021;325:1403. [PMID: 33625476]
Walsh K et al. Health advice and education given to overweight patients by primary care doctors and nurses: a scoping literature review. Prev Med Rep. 2019;14:100812. [PMID: 30805277]

CANCER PREVENTION

Primary Prevention

Persons who engage in regular physical exercise and avoid obesity have lower rates of breast and colon cancer. Chemoprevention has been widely studied for primary cancer prevention without clear evidence of benefits (see earlier Chemoprevention section and Chapter 39). Use of tamoxifen, raloxifene, and aromatase inhibitors for breast cancer prevention is discussed in Chapters 17 and 39. Hepatitis B vaccination can prevent HCC. Screening and treatment of hepatitis C is another strategy to prevent HCC (see Chapter 16); new recommendations have extended the population eligible for screening. HPV virus-like particle (VLP) vaccine is recommended to prevent cervical cancer (Table 1–3). HPV vaccines may also have a role in the prevention of HPV-related head and neck and possibly anal cancers. The USPSTF recommends genetic counseling and, if indicated after counseling, genetic testing for women whose family or personal history is associated with an increased risk of harmful mutations in the *BRCA 1/2* gene. Guidelines for optimal cancer screening in adults over the age of 75 are unsettled; thus, an individualized approach that considers differences in disease risk rather than chronological age alone is recommended.

Athanasiou A et al. HPV vaccination and cancer prevention. Best Pract Res Clin Obstet Gynaecol. 2020;65:109. [PMID: 32284298]
US Preventive Services Task Force; Owens DK et al. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2019;322:652. [PMID: 31429903]

Screening & Early Detection

Screening prevents death from cancers of the breast, colon, and cervix. Current cancer screening recommendations from the USPSTF are available online at https://www.uspreventiveservicestaskforce.org/BrowseRec/Index/browse-recommendations. Despite an increase in rates of screening for breast, cervical, and colon cancer over the last decade, overall screening for these cancers is suboptimal.

Though breast cancer mortality is reduced with mammography screening, screening mammography has both benefits and downsides. Clinicians should discuss the risks and benefits with each patient and consider individual patient preferences when deciding when to begin screening (see Chapters 17 and e6).

Screening for testicular cancers among asymptomatic adolescent or adult males is not recommended by the USPSTF. Prostate cancer screening remains controversial, since no completed trials have answered the question of whether early detection and treatment after screen detection produce sufficient benefits to outweigh harms of treatment. For men between the ages of 55 and 69, the decision to screen should be individualized and include a discussion of its risks and benefits with a clinician. The USPSTF recommends against PSA-based prostate cancer screening for men older than age 70 years (grade D recommendation).

The USPSTF recommends colorectal cancer screening for adults aged 45–75 years and selectively screening adults aged 76–85 years (considering the patient's overall health, prior screening history, and patient's preferences).

Annual or biennial fecal occult blood testing reduces mortality from colorectal cancer. Fecal immunochemical tests (FIT) are superior to guaiac-based fecal occult blood tests (gFOBT) in detecting advanced adenomatous polyps and colorectal cancer, and patients are more likely to favor FIT over gFOBT. CT colonography (virtual colonoscopy) is a noninvasive option in screening for colorectal cancer. It has been shown to have a high safety profile and performance similar to colonoscopy.

The USPSTF recommends screening for cervical cancer in women aged 21–65 years with a Papanicolaou smear (cytology) every 3 years or, for women aged 30–65 years who desire longer intervals, screening with cytology and HPV testing every 5 years. The American Cancer Society recommends screening for people aged 25–65 years with primary HPV testing every 5 years. The USPSTF recommends against screening in women younger than 21 years of age and average-risk women over 65 with adequate negative prior screenings. Receipt of HPV vaccination has no impact on screening intervals.

Women whose cervical specimen HPV tests are positive but cytology results are otherwise negative should repeat co-testing in 12 months (option 1) or undergo HPV-genotype–specific testing for types 16 or 16/18 (option 2). Colposcopy is recommended in women who test positive

for types 16 or 16/18. Women with atypical squamous cells of undetermined significance (ASCUS) on cytology and a negative HPV test result should continue routine screening as per age-specific guidelines.

The USPSTF recommends offering annual lung cancer screening with low-dose CT to current smokers aged 50 to 80 years and 20-pack-year smoking history or to smokers who quit within the past 15 years. Screening should stop once a person has not smoked for 15 years or a health problem that significantly limits life expectancy has developed. Screening should not be viewed as an alternative to smoking cessation but rather as a complementary approach.

Fontham ETH et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin. 2020;70:321. [PMID: 32729638]
Jonas DE et al. Screening for lung cancer with low-dose computed tomography: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2021;325:971. [PMID: 33687468]
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US Preventive Services Task Force; Curry SJ et al. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018;320:674. [PMID: 30140884]
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US Preventive Services Task Force; Grossman DC et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018;319:1901. [PMID: 29801017]
US Preventive Services Task Force; Krist AH. Screening for lung cancer: US Preventive Services Task Force recommendation statement. JAMA. 2021;325:962. [PMID: 33687470]

PREVENTION OF INJURIES & VIOLENCE

Injuries remain the most important cause of loss of potential years of life before age 65. Homicide and motor vehicle accidents are a major cause of injury-related deaths among young adults, and accidental falls are the most common cause of injury-related death in older adults. Approximately one-third of all injury deaths include a diagnosis of traumatic brain injury, which has been associated with an increased risk of suicide. Although motor vehicle accident deaths per miles driven have declined in the United States, there has been an increase in motor vehicle accidents related to distracted driving (using a cell phone, texting, eating).

Men ages 16–35 are at especially high risk for serious injury and death from accidents and violence, with Black and Latino men at greatest risk. Deaths from firearms have reached epidemic levels in the United States. Having a gun in the home increases the likelihood of homicide nearly threefold and of suicide fivefold. Educating clinicians to recognize and treat depression as well as restricting access to lethal methods have been found to reduce suicide rates.

Clinicians have a critical role in the detection, prevention, and management of intimate partner violence (see Chapter e6). The USPSTF recommends screening women of childbearing age for intimate partner violence and providing or referring women to intervention services when needed. Inclusion of a single question in the medical history—"At any time, has a partner ever hit you, kicked you, or otherwise physically hurt you?"—can increase identification of this common problem. Assessment for abuse and offering of referrals to community resources create the potential to interrupt and prevent recurrence of domestic violence and associated trauma. Clinicians should take an active role in following up with patients whenever possible, since intimate partner violence screening with passive referrals to services may not be adequate.

Physical and psychological abuse, exploitation, and neglect of older adults are serious, underrecognized problems; they may occur in up to 10% of elders. Risk factors for elder abuse include a culture of violence in the family; a demented, debilitated, or depressed and socially isolated victim; and a perpetrator profile of mental illness, alcohol or drug abuse, or emotional and/or financial dependence on the victim. Clues to elder mistreatment include the patient's ill-kempt appearance, recurrent urgent-care visits, missed appointments, suspicious physical findings, and implausible explanations for injuries.

Cimino-Fiallos N et al. Elder abuse—a guide to diagnosis and management in the emergency department. Emerg Med Clin North Am. 2021;39:405. [PMID: 33863468]
Kirk L et al. What barriers prevent health professionals screening women for domestic abuse? A literature review. Br J Nurs. 2020;29:754. [PMID: 32649247]
Mercier É et al. Elder abuse in the out-of-hospital and emergency department settings: a scoping review. Ann Emerg Med. 2020;75:181. [PMID: 31959308]

PREVENTION OF SUBSTANCE USE DISORDER: ALCOHOL & ILLICIT DRUGS

Unhealthy alcohol use is a major public health problem in the United States, where approximately 51% of adults 18 years and older are current regular drinkers (at least 12 drinks in the past year). The spectrum of alcohol use disorders includes alcohol dependence, harmful pattern use of alcohol, and entities such as alcohol intoxication, alcohol withdrawal, and several alcohol-induced mental disorders. The ICD-11 includes a new category: hazardous alcohol use. Categorized as a risk factor, hazardous alcohol use is a pattern of alcohol use that appreciably increases the risk of physical or mental health harmful consequences to the user.

Underdiagnosis and undertreatment of alcohol misuse is substantial, both because of patient denial and lack of detection of clinical clues.

As with cigarette use, clinician identification and counseling about unhealthy alcohol use are essential. The USPSTF recommends screening adults aged 18 years and older for unhealthy alcohol use. The National Institute on Alcohol Abuse and Alcoholism recommends the following single-question screening test (validated in primary care settings): "How many times in the past year have you had X or more drinks in a day?" (X is 5 for men and 4 for women, and a response of more than 1 time is considered positive.)

Those who screen positive on the single-item questionnaire should complete the Alcohol Use Disorder

Identification Test (AUDIT), which consists of questions on the quantity and frequency of alcohol consumption, on alcohol dependence symptoms, and on alcohol-related problems (Table 1–7).

Clinicians should provide those who screen positive for hazardous or risky drinking with brief behavioral counseling interventions to reduce alcohol misuse. Use of screening procedures and brief intervention methods (see Chapter 25) can produce a 10–30% reduction in long-term alcohol use and alcohol-related problems. Those whose AUDIT scores suggest alcohol use disorder (AUDIT > 12) should undergo more extensive evaluation and potential referral for treatment.

Deaths due to opioid overdose have dramatically increased. Opioid risk mitigation strategies include use of risk assessment tools, treatment agreements (contracts), and urine drug testing. Additional strategies include establishing and strengthening prescription drug monitoring programs, regulating pain management facilities, and establishing dosage thresholds requiring consultation with pain specialists. Medication-assisted treatment, the use of medications with counseling and behavioral therapy, is effective in the prevention of opioid overdose and substance abuse disorders. Methadone, buprenorphine, and naltrexone are FDA approved for use in medication-assisted treatment. Buprenorphine has potential as a medication to ameliorate the symptoms and signs of withdrawal from opioids and is effective in reducing concomitant cocaine and opioid abuse. The FDA supports greater access to naloxone and is currently exploring options to make naloxone more available to treat opioid overdose. (See Chapter 5.)

Use of illegal drugs—including cocaine, methamphetamine, and so-called designer drugs—either sporadically or episodically remains an important problem. Lifetime prevalence of drug abuse is approximately 8% and is generally greater among men, young and unmarried individuals, Native Americans, and those of lower socioeconomic status. As with alcohol, drug abuse disorders often coexist with personality disorders, anxiety disorders, and other substance abuse disorders.

Clinical aspects of substance abuse are discussed in Chapter 25.

Chou R et al. Interventions for unhealthy drug use—supplemental report: a systematic review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020 Jun. Report No.: 19-05255-EF-2. https://www.ncbi.nlm.nih.gov/books/NBK558205/ [PMID: 32550674]

Table 1–7. Screening for alcohol abuse using the Alcohol Use Disorder Identification Test (AUDIT).

(Scores for response categories are given in parentheses. Added together, Total Scores range from 0 to 40, with scores of 1 to 7 suggesting low-risk drinking; 8 to 14, hazardous or harmful drinking; and >15, alcohol dependence.)				
1. How often do you have a drink containing alcohol?				
(0) Never	(1) Monthly or less	(2) Two to four times a month	(3) Two or three times a week	(4) Four or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?				
(0) 1 or 2	(1) 3 or 4	(2) 5 or 6	(3) 7 to 9	(4) 10 or more
3. How often do you have six or more drinks on one occasion?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost daily
4. How often during the past year have you found that you were not able to stop drinking once you had started?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost daily
5. How often during the past year have you failed to do what was normally expected of you because of drinking?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost daily
6. How often during the past year have you needed a first drink in the morning to get yourself going after a heavy drinking session?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost daily
7. How often during the past year have you had a feeling of guilt or remorse after drinking?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost daily
8. How often during the past year have you been unable to remember what happened the night before because you had been drinking?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost daily
9. Have you or has someone else been injured as a result of your drinking?				
(0) No		(2) Yes, but not in the past year		(4) Yes, during the past year
10. Has a relative or friend or a doctor or other health worker been concerned about your drinking or suggested you cut down?				
(0) No		(2) Yes, but not in the past year		(4) Yes, during the past year

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Saunders JB et al. Alcohol use disorders in ICD-11: past, present, and future. Alcohol Clin Exp Res. 2019;43:1617. [PMID: 31194891]

Substance Abuse and Mental Health Services Administration (SAMHSA). Medication-Assisted Treatment (MAT). https://www.samhsa.gov/medication-assisted-treatment

Common Symptoms

2

Paul L. Nadler, MD
Ralph Gonzales, MD, MSPH

COUGH

ESSENTIAL INQUIRIES

- Age, occupational history, environmental exposures, risk of infection with SARS-CoV-2, and duration of cough.
- Use of tobacco, cannabis, e-cigarettes (vaping).
- Dyspnea (at rest or with exertion).
- Vital signs (heart rate, respiratory rate, body temperature); pulse oximetry.
- Chest examination.
- Chest radiography, especially when unexplained cough lasts > 3–6 weeks.

General Considerations

Cough is the most common symptom for which patients seek medical attention. Cough results from stimulation of mechanical or chemical afferent nerve receptors in the bronchial tree. Effective cough depends on an intact afferent–efferent reflex arc, adequate expiratory and chest wall muscle strength, and normal mucociliary production and clearance.

Clinical Findings

A. Symptoms

Distinguishing **acute** (less than 3 weeks), **persistent** (3–8 weeks), and **chronic** (more than 8 weeks) cough illness syndromes is a useful first step in evaluation. Postinfectious cough lasting 3–8 weeks has also been referred to as **subacute** cough to distinguish this common, distinct clinical entity from acute and chronic cough.

1. Acute cough—In healthy adults, most acute cough syndromes are due to viral respiratory tract infections. Additional features of infection such as fever, nasal congestion, and sore throat help confirm this diagnosis. Dyspnea (at rest or with exertion) may reflect a more serious condition, and further evaluation should include assessment of oxygenation (pulse oximetry or arterial blood gas measurement), airflow (peak flow or spirometry), and pulmonary parenchymal disease (chest radiography). The timing and character of the cough are not very useful in establishing the cause of acute cough syndromes, although cough-variant asthma should be considered in adults with prominent nocturnal cough, and persistent cough with phlegm increases the likelihood of COPD. The presence of posttussive emesis or inspiratory whoop in adults modestly increases the likelihood of pertussis, and the absence of paroxysmal cough and the presence of fever decrease its likelihood. Loss of smell or taste accompanying a new cough illness is specific but not sensitive for COVID-19 infection. Uncommon causes of acute cough should be suspected in those with HF or hay fever (allergic rhinitis) and those with occupational risk factors (such as farmworkers).

2. Persistent and chronic cough—Cough due to acute respiratory tract infection resolves within 3 weeks in more than 90% of patients. Pertussis should be considered in adolescents and adults who have persistent or severe cough lasting more than 3 weeks, who have not been adequately boosted with Tdap, and who have been exposed to a person with confirmed pertussis. It should also be considered in geographic areas where the prevalence of pertussis approaches 20% (although its exact prevalence is difficult to ascertain due to the limited sensitivity of diagnostic tests).

When ACE inhibitor use, acute respiratory tract infection, and chest radiographic abnormalities are absent, most cases of persistent and chronic cough are related to postnasal drip (upper airway cough syndrome), cough-variant asthma, or GERD, or some combination of these three entities. Approximately 10% of cases are caused by nonasthmatic eosinophilic bronchitis. A history of nasal or sinus congestion, wheezing, or heartburn should direct subsequent evaluation and treatment, though these conditions frequently cause persistent cough in the absence of typical symptoms. Dyspnea at rest or with exertion is not commonly reported among patients with persistent cough;

dyspnea requires assessment for chronic lung disease, HF, anemia, PE, or pulmonary hypertension.

Bronchogenic carcinoma is suspected when cough is accompanied by unexplained weight loss, hemoptysis, and fevers with night sweats, particularly in persons with significant tobacco or occupational exposures (asbestos, radon, diesel exhaust, and metals). Persistent and chronic cough accompanied by excessive mucus secretions increases the likelihood of COPD, particularly if there is a history of cigarette smoking, or of bronchiectasis if accompanied by a history of recurrent or complicated pneumonia; chest radiographs are helpful in diagnosis. Chronic cough with dry eyes may represent Sjögren syndrome. A chronic dry cough may be the first symptom of idiopathic pulmonary fibrosis.

B. Physical Examination

Pneumonia is suspected when acute cough is accompanied by vital sign abnormalities (tachycardia, tachypnea, fever). Findings suggestive of airspace consolidation (crackles, decreased breath sounds, fremitus, egophony) are significant predictors of community-acquired pneumonia but are present in a minority of cases. Purulent sputum is associated with bacterial infections in patients with structural lung disease (eg, COPD, cystic fibrosis), but it is a poor predictor of pneumonia in the otherwise healthy adult. Wheezing and rhonchi are frequent findings in adults with acute bronchitis and do not indicate consolidation or adult-onset asthma in most cases.

Examination of patients with persistent cough should include a search for chronic sinusitis, which may contribute to postnasal drip syndrome or to asthma. Physical examination may help distinguish COPD from HF. In patients with cough and dyspnea, a normal match test (ability to blow out a match from 25 cm away) and maximum laryngeal height greater than 4 cm (measured from the sternal notch to the cricoid cartilage at end expiration) substantially decrease the likelihood of COPD. Similarly, normal jugular venous pressure and no hepatojugular reflux decrease the likelihood of biventricular HF.

C. Diagnostic Studies

1. Acute cough—Chest radiography should be considered for any adult with acute cough whose vital signs are abnormal or whose chest examination suggests pneumonia. The relationship between specific clinical findings and the probability of pneumonia is shown in Table 2–1. A large, multicenter randomized clinical trial found that elevated serum CRP (levels greater than 30 mg/dL) improves diagnostic accuracy of clinical prediction rules for pneumonia in adults with acute cough; serum procalcitonin had only marginal utility in outpatient management (in contrast with severe pneumonia requiring hospital care). A meta-analysis found that lung ultrasonography had better accuracy than chest radiography for the diagnosis of adult community-acquired pneumonia. Lung ultrasonography had a pooled sensitivity of 0.95 and a specificity of 0.90. Chest radiography had a pooled sensitivity of 0.77 and a specificity of 0.91. In patients with dyspnea, pulse oximetry and peak flow help exclude hypoxemia or obstructive airway disease. However, a normal pulse oximetry value (eg, greater than 93%) does not rule out a significant alveolar–arterial (A–a) gradient when patients have effective respiratory compensation. During documented outbreaks, clinical diagnosis of influenza has a positive predictive value of ~70%; this usually obviates the need for rapid diagnostic tests.

Table 2–1. Positive and negative likelihood ratios of history, physical examination, and laboratory findings for the diagnosis of pneumonia.

Finding	Positive LR	Negative LR
Medical history		
Fever	1.7–2.1	0.6–0.7
Chills	1.3–1.7	0.7–0.9
Physical examination		
Tachypnea (respiratory rate > 25 breaths/min)	1.5–3.4	0.8
Tachycardia (> 100 beats/min in two studies or > 120 beats/min in one study)	1.6–2.3	0.5–0.7
Hyperthermia (> 37.8°C)	1.4–4.4	0.6–0.8
Chest examination		
Dullness to percussion	2.2–4.3	0.8–0.9
Decreased breath sounds	2.3–2.5	0.6–0.8
Crackles	1.6–2.7	0.6–0.9
Rhonchi	1.4–1.5	0.8–0.9
Egophony	2.0–8.6	0.8–1.0
Laboratory findings		
Leukocytosis (> 11,000/mcL [11 × 10^9/L] in one study or ≥ 10,400/mcL [10.4 × 10^9/L] in another study)	1.9–3.7	0.3–0.6

2. Persistent and chronic cough—Chest radiography is indicated when ACE inhibitor therapy–related and postinfectious cough are excluded. If pertussis is suspected, PCR testing should be performed on a nasopharyngeal swab or nasal wash specimen—although the ability to detect pertussis decreases as the duration of cough increases. When the chest film is normal, postnasal drip, asthma, or GERD are the most likely causes. The presence of typical symptoms of these conditions directs further evaluation or empiric therapy, though typical symptoms are often absent. Definitive tests for determining the presence of each are available (Table 2–2). However, empiric treatment with a maximum-strength regimen for postnasal drip, asthma, or GERD for 2–4 weeks is one recommended approach since documenting the presence of postnasal drip, asthma, or GERD does not mean they are the cause of the cough. Alternative approaches to identifying patients who have corticosteroid-responsive cough due to asthma include examining induced sputum for increased eosinophil counts

Table 2–2. Empiric therapy or definitive testing for persistent cough.

Suspected Condition	Step 1 (Empiric Therapy)	Step 2 (Definitive Testing)
Postnasal drip	Therapy for allergy or chronic sinusitis	Sinus CT scan; otolaryngologic referral
Asthma	Beta-2-agonist	Spirometry; consider methacholine challenge if normal
GERD	Lifestyle and diet modifications with or without PPIs	Esophageal pH monitoring

(greater than 3%) or providing an empiric trial of prednisone, 30 mg daily orally for 2 weeks.

Nonasthmatic eosinophilic bronchitis can be diagnosed by finding eosinophils with induced sputum analysis after the exclusion of other causes for chronic cough by clinical, radiologic, and lung function assessment. The cough usually responds well to inhaled corticosteroids.

Spirometry may help measure large airway obstruction (eg, foreign body or cancer) in patients who have persistent cough and wheezing and who are not responding to asthma treatment. When empiric treatment trials are not successful, additional evaluation with pH manometry, endoscopy, barium swallow, sinus CT, or high-resolution chest CT may identify the cause.

Differential Diagnosis

A. Acute Cough

Acute cough may be a symptom of acute respiratory tract infection, COVID-19, asthma, allergic rhinitis, HF, and ACE inhibitor therapy, as well as many less common causes.

B. Persistent and Chronic Cough

Causes of persistent cough include environmental exposures (cigarette smoke, air pollution), occupational exposures, pertussis, postnasal drip, asthma (including cough-variant asthma), GERD, COPD, chronic aspiration, bronchiectasis, nonasthmatic eosinophilic bronchitis, tuberculosis or other chronic infection, interstitial lung disease, and bronchogenic carcinoma. COPD is a common cause of persistent cough among patients older than 50 years who have been cigarette smokers. Persistent cough may also be due to somatic cough syndrome or tic cough, or vocal fold dysfunction.

C. Cough in the Immunocompromised Patient

The evaluation of cough in immunocompromised patients is the same as in immunocompetent patients but with an increased concern for tuberculosis (regardless of radiographic findings) as well as fungi, cytomegalovirus, varicella, herpesvirus, and *Pneumocystis jirovecii*.

Treatment

A. Acute Cough

Treatment of acute cough should target the underlying etiology of the illness, the cough reflex itself, and any additional factors that exacerbate the cough. Cough duration is typically 1–3 weeks, yet patients frequently expect cough to last fewer than 10 days. Limited studies on the use of dextromethorphan suggest a minor or modest benefit. Honey may provide symptomatic benefit.

When influenza is diagnosed (including H1N1 influenza), oral oseltamivir or zanamivir or intravenous peramivir are equally effective (1 less day of illness) when initiated within 30–48 hours of illness onset; treatment is recommended regardless of illness duration when patients have severe, complicated, or progressive influenza and in patients requiring hospitalization. In *Chlamydophila*- or *Mycoplasma*-documented infection or outbreaks, first-line antibiotics include erythromycin or doxycycline. Antibiotics do not improve cough severity or duration in patients with uncomplicated acute bronchitis. In patients with bronchitis and wheezing, inhaled beta-2-agonist therapy reduces severity and duration of cough. In patients with acute cough, treating the accompanying postnasal drip (with antihistamines, decongestants, saline nasal irrigation, or nasal corticosteroids) can be helpful. Two studies (n = 163 total patients) found codeine to be no more effective than placebo in reducing acute cough symptoms.

B. Persistent and Chronic Cough

Evaluation and management of persistent cough often require multiple visits and therapeutic trials, which frequently lead to frustration, anger, and anxiety. When pertussis infection is suspected early in its course, treatment with a macrolide antibiotic (see Chapter 33) is appropriate to reduce organism shedding and transmission. When pertussis has lasted more than 7–10 days, antibiotic treatment does not affect the duration of cough, which can last up to 6 months. Early identification, revaccination with Tdap, and treatment are encouraged for adult patients who work or live with persons at high risk for complications from pertussis (pregnant women, infants [particularly younger than 1 year], and immunosuppressed individuals).

Table 2–2 outlines empiric treatments for persistent cough. There is no evidence to guide how long to continue treatment for persistent cough due to postnasal drip, asthma, or GERD. Studies have not found a consistent benefit of inhaled corticosteroid therapy in adults with persistent cough.

There is insufficient evidence to recommend the routine use of any pharmacologic treatments (antibiotics, bronchodilators, mucolytics) as a means of relieving cough for adult patients with chronic cough due to stable chronic bronchitis.

When empiric treatment trials fail, consider other causes of chronic cough such as obstructive sleep apnea, tonsillar or uvular enlargement, and environmental fungi (see Chapter 36). The small percentage of patients with idiopathic chronic cough should be managed in

consultation with an otolaryngologist or a pulmonologist; consider a high-resolution CT scan of the lungs. Treatment options include nebulized lidocaine therapy and morphine sulfate, 5–10 mg orally twice daily. Sensory dysfunction of the laryngeal branches of the vagus nerve may contribute to persistent cough syndromes and may help explain the effectiveness of gabapentin in patients with chronic cough. Baclofen may have similar neuromodulatory action and benefit as gabapentin.

Speech pathology therapy combined with pregabalin has some benefit in chronic refractory cough. In patients with cough hypersensitivity syndrome, therapy aimed at shifting the patient's attentional focus from internal stimuli to external focal points can be helpful. PPIs are not effective when used in isolation for treating chronic cough due to gastroesophageal reflux; most benefit appears to come from lifestyle modifications and weight reduction.

When to Refer

- Failure to control persistent or chronic cough following empiric treatment trials.
- Patients with recurrent symptoms should be referred to an otolaryngologist, pulmonologist, or gastroenterologist.

When to Admit

- Patient at high risk for tuberculosis for whom compliance with respiratory precautions is uncertain.
- Need for urgent bronchoscopy, such as suspected foreign body.
- Smoke or toxic fume inhalational injury.
- Gas exchange is impaired by cough.
- Patients at high risk for barotrauma (eg, recent pneumothorax).

Kardos P et al. German Respiratory Society guidelines for diagnosis and treatment of adults suffering from acute, subacute and chronic cough. Respir Med. 2020;170:105939. [PMID: 32843157]

Malesker MA et al; CHEST Expert Cough Panel. Chronic cough due to stable chronic bronchitis: CHEST Expert Panel Report. Chest. 2020;158:705. [PMID: 32105719]

Smith MP et al; CHEST Expert Cough Panel. Acute cough due to acute bronchitis in immunocompetent adult outpatients: CHEST Expert Panel Report. Chest. 2020;157:1256. [PMID: 32092323]

DYSPNEA

ESSENTIAL INQUIRIES

- Fever, cough, risk of COVID-19, and chest pain.
- Vital sign measurements; pulse oximetry.
- Cardiac and chest examination.
- Chest radiography and arterial blood gas measurement in selected patients.

General Considerations

Dyspnea is a subjective experience or perception of uncomfortable breathing. The relationship between level of dyspnea and the severity of underlying disease varies widely among individuals. Dyspnea can result from conditions that increase the mechanical effort of breathing (eg, asthma, COPD, restrictive lung disease, respiratory muscle weakness), alveolar lung disease (pulmonary edema, pneumonia, alveolar proteinosis), conditions that produce compensatory tachypnea (eg, hypoxemia, acidosis), primary pulmonary vasculopathy (pulmonary hypertension), or psychogenic conditions.

Clinical Findings

A. Symptoms

The duration, severity, and periodicity of dyspnea influence the tempo of the clinical evaluation. Rapid onset or severe dyspnea in the absence of other clinical features should raise concern for pneumothorax, PE, or increased left ventricular end-diastolic pressure (LVEDP).

Spontaneous pneumothorax is usually accompanied by chest pain and occurs most often in thin, young males and in those with underlying lung disease. PE should always be suspected when a patient with new dyspnea reports a recent history (previous 4 weeks) of prolonged immobilization or surgery, estrogen therapy, or other risk factors for DVT (eg, previous history of thromboembolism, cancer, obesity, lower extremity trauma) and when the cause of dyspnea is not apparent. Silent MI, which occurs more frequently in persons with diabetes and women, can result in increased LVEDP, acute HF, and dyspnea.

Accompanying symptoms provide important clues to causes of dyspnea. When cough and fever are present, pulmonary disease (particularly infection) is the primary concern; myocarditis, pericarditis, and septic emboli can also present in this manner. Chest pain should be further characterized as acute or chronic, pleuritic or exertional. Although acute pleuritic chest pain is the rule in acute pericarditis and pneumothorax, most patients with pleuritic chest pain in the outpatient clinic have pleurisy due to acute viral respiratory tract infection. Periodic chest pain that precedes the onset of dyspnea suggests myocardial ischemia or PE. Most cases of dyspnea associated with wheezing are due to acute bronchitis; however, other causes include new-onset asthma, foreign body, and vocal fold dysfunction. Interstitial lung disease and pulmonary hypertension should be considered in patients with symptoms (or history) of connective tissue disease. Pulmonary lymphangitic carcinomatosis should be considered if a patient has a malignancy, especially breast, lung, or gastric cancer.

When a patient reports prominent dyspnea with mild or no accompanying features, consider noncardiopulmonary causes of impaired oxygen delivery (anemia, methemoglobinemia, cyanide ingestion, carbon monoxide poisoning), metabolic acidosis, panic disorder, neuromuscular disorders, and chronic PE.

Platypnea-orthodeoxia syndrome is characterized by dyspnea and hypoxemia on sitting or standing that

improves in the recumbent position. Hyperthyroidism can cause dyspnea from increased ventilatory drive, respiratory muscle weakness, or pulmonary hypertension. Patients in whom moderate to severe SARS-CoV-2 disease develops typically have 4–10 days of upper respiratory infection symptoms followed by a precipitous increase in dyspnea. Patients who recover from their initial COVID-19 infection may have persistent dyspnea as part of the "long COVID" syndrome.

B. Physical Examination

A focused physical examination should include evaluation of the head and neck, chest, heart, and lower extremities. Visual inspection of the patient can suggest obstructive airway disease (pursed-lip breathing, use of accessory respiratory muscles, barrel-shaped chest), pneumothorax (asymmetric excursion), or metabolic acidosis (Kussmaul respirations). Patients with impending upper airway obstruction (eg, epiglottitis, foreign body) or severe asthma exacerbation sometimes assume a tripod position. Focal wheezing raises the suspicion for a foreign body or other bronchial obstruction. Maximum laryngeal height (the distance between the top of the thyroid cartilage and the suprasternal notch at end expiration) is a measure of hyperinflation. Obstructive airway disease is virtually nonexistent when a nonsmoking patient younger than age 45 years has a maximum laryngeal height greater than 4 cm.

Factors increasing the likelihood of obstructive airway disease (in patients without known obstructive airway disease) include patient history of more than 40 pack-years smoking (adjusted LR+ 11.6; LR– 0.9), patient age 45 years or older (LR+ 1.4; LR– 0.5), and maximum laryngeal height greater than or equal to 4 cm (LR+ 3.6; LR– 0.7). With all three of these factors present, the LR+ rises to 58.5 and the LR– falls to 0.3.

Absent breath sounds suggest a pneumothorax. An accentuated pulmonic component of the second heart sound (loud P_2) is a sign of pulmonary hypertension and PE.

Clinical predictors of increased LVEDP in dyspneic patients with no prior history of HF include tachycardia, systolic hypotension, jugular venous distention, hepatojugular reflux, bibasilar crackles, third heart sound, lower extremity edema, and chest film findings of pulmonary vascular redistribution or cardiomegaly. When none is present, there is a very low probability (less than 10%) of increased LVEDP, but when two or more are present, there is a very high probability (greater than 90%) of increased LVEDP.

C. Diagnostic Studies

Causes of dyspnea that can be managed without chest radiography are few: anemia, carbon monoxide poisoning, and ingestions causing lactic acidosis and methemoglobinemia. The diagnosis of pneumonia should be confirmed by chest radiography in most patients, and elevated blood levels of procalcitonin or CRP can support the diagnosis of pneumonia in equivocal cases or in the presence of interstitial lung disease. Conversely, a low procalcitonin can help exclude pneumonia in dyspneic patients presenting with HF.

Chest radiography is fairly sensitive and specific for new-onset HF (represented by redistribution of pulmonary venous circulation) and can help guide treatment of patients with other cardiac diseases. NT-proBNP can assist in the diagnosis of HF (see below). End-expiratory chest radiography enhances detection of small pneumothoraces. A systematic review of five randomized controlled trials and 44 prospective cohort-type studies in patients with acute dyspnea assessed point-of-care ultrasonography (POCUS) as a diagnostic tool to determine the underlying cause of dyspnea. When added to a standard diagnostic pathway, POCUS led to statistically significantly more correct diagnoses in patients with dyspnea than the standard diagnostic pathway. POCUS consistently improved the sensitivities of standard diagnostic pathways to detect HF, pneumonia, PE, pleural effusion, or pneumothorax. Specificities increased in most studies; in-hospital mortality and length of hospital stay, however, did not differ significantly between patients who did or did not receive POCUS in addition to standard diagnostic tests.

A normal chest radiograph has substantial diagnostic value. When there is no physical examination evidence of COPD or HF and the chest radiograph is normal, the major remaining causes of dyspnea include PE, *P jirovecii* infection (the initial radiograph may be normal in up to 25%), upper airway obstruction, foreign body, anemia, and metabolic acidosis. If a patient has tachycardia or hypoxemia but a normal chest radiograph and ECG, then tests to exclude pulmonary emboli, anemia, or metabolic acidosis are warranted. High-resolution chest CT is particularly useful in the evaluation of interstitial and alveolar lung disease. Helical ("spiral") CT is useful to diagnose PE since the images are high resolution and require only one breath-hold by the patient, but to minimize unnecessary testing and radiation exposure, the clinician should first consider a clinical decision rule (with or without D-dimer testing) to estimate the pretest probability of a PE. It is appropriate to forego CT scanning in patients with very low probability of pulmonary embolus when other causes of dyspnea are more likely (see Chapter 9).

Laboratory findings suggesting increased LVEDP include elevated serum BNP or NT-proBNP levels. BNP has been shown to reliably diagnose severe dyspnea caused by HF and to differentiate it from dyspnea due to other conditions.

Arterial blood gas measurement may be considered if clinical examination and routine diagnostic testing are equivocal. With two notable exceptions (carbon monoxide poisoning and cyanide toxicity), arterial blood gas measurement distinguishes increased mechanical effort causes of dyspnea (respiratory acidosis with or without hypoxemia) from compensatory tachypnea (respiratory alkalosis with or without hypoxemia or metabolic acidosis) and from psychogenic dyspnea (respiratory alkalosis). Carbon monoxide and cyanide impair oxygen delivery with minimal alterations in Po_2; percent carboxyhemoglobin identifies carbon monoxide toxicity. Cyanide poisoning should be considered in a patient with profound lactic acidosis following exposure to burning vinyl (such as a theater fire or industrial accident). Suspected carbon monoxide

poisoning or methemoglobinemia can also be confirmed with venous carboxyhemoglobin or methemoglobin levels. Venous blood gas testing is also an option for assessing acid-base and respiratory status by measuring venous pH and Pco_2 but is unable to provide information on oxygenation status. To correlate with arterial blood gas values, venous pH is typically 0.03–0.05 units lower, and venous Pco_2 is typically 4–5 mm Hg higher than arterial samples.

Because arterial blood gas testing is impractical in most outpatient settings, pulse oximetry has a central role in the office evaluation of dyspnea. Oxygen saturation values above 96% almost always correspond with a Po_2 greater than 70 mm Hg, whereas values less than 94% may represent clinically significant hypoxemia. Important exceptions to this rule include carbon monoxide toxicity, which leads to a normal oxygen saturation (due to the similar wavelengths of oxyhemoglobin and carboxyhemoglobin), and methemoglobinemia, which results in an oxygen saturation of about 85% that fails to increase with supplemental oxygen. Pulse oximetry to detect occult hypoxia is less accurate in Black patients (OR, 2.57) compared to White patients. A delirious or obtunded patient with obstructive lung disease warrants immediate measurement of arterial blood gases to exclude hypercapnia and the need for intubation, regardless of the oxygen saturation. If a patient reports dyspnea with exertion, but resting oximetry is normal, assessment of desaturation with ambulation (eg, a brisk walk around the clinic) can be useful for confirming impaired gas exchange. Persons with COVID-19 may have low oxygen saturation with minimal dyspnea and profound desaturation with minimal exertion.

A study found that for adults without known cardiac or pulmonary disease reporting dyspnea on exertion, spirometry, NT-proBNP, and CT imaging were the most informative tests.

Episodic dyspnea can be challenging if an evaluation cannot be performed during symptoms. Life-threatening causes include recurrent PE, myocardial ischemia, and reactive airway disease. When associated with audible wheezing, vocal fold dysfunction should be considered, particularly in a young woman who does not respond to asthma therapy. Spirometry is very helpful in further classifying patients with obstructive airway disease but is rarely needed in the initial or emergent evaluation of patients with acute dyspnea.

Differential Diagnosis

Urgent and emergent conditions causing acute dyspnea include pneumonia, COPD, asthma, pneumothorax, PE, cardiac disease (eg, HF, acute MI, valvular dysfunction, arrhythmia, intracardiac shunt), pleural effusion, COVID-19, diffuse alveolar hemorrhage, metabolic acidosis, cyanide toxicity, methemoglobinemia, and carbon monoxide poisoning. Chronic dyspnea may be caused by interstitial lung disease, pulmonary hypertension, or pulmonary alveolar proteinosis.

Treatment

The treatment of urgent or emergent causes of dyspnea should aim to relieve the underlying cause. Pending diagnosis, patients with hypoxemia should be immediately provided supplemental oxygen unless significant hypercapnia is present or strongly suspected pending arterial blood gas measurement. Dyspnea frequently occurs in patients nearing the end of life. Opioid therapy, anxiolytics, and corticosteroids can provide substantial relief independent of the severity of hypoxemia. However, inhaled opioids are not effective.

Oxygen therapy is most beneficial to patients with significant hypoxemia (Pao_2 less than 55 mm Hg) (see Chapter 5). In patients with severe COPD and hypoxemia, oxygen therapy improves exercise performance and mortality. Pulmonary rehabilitation programs are another therapeutic option for patients with moderate to severe COPD or interstitial pulmonary fibrosis. Noninvasive ventilation may be considered for patients with dyspnea caused by an acute COPD exacerbation.

When to Refer

- Following acute stabilization, patients with advanced COPD should be referred to a pulmonologist, and patients with HF or valvular heart disease should be referred to a cardiologist.
- Cyanide toxicity or carbon monoxide poisoning should be managed in conjunction with a toxicologist.
- Lung transplantation can be considered for patients with advanced interstitial lung disease.

When to Admit

- Impaired gas exchange from any cause or high risk of PE pending definitive diagnosis.
- Suspected cyanide toxicity or carbon monoxide poisoning.

Corson-Knowles DR et al. In outpatients, low or moderate clinical pretest probability with probability-defined D-dimer cut points ruled out PE. Ann Intern Med. 2020;172:JC47. [PMID: 32311731]

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Valbuena VSM et al. Racial bias in pulse oximetry measurement among patients about to undergo ECMO in 2019–2020, a retrospective cohort study. Chest. 2021 Sep 27. [Epub ahead of print] [PMID: 34592317]

HEMOPTYSIS

ESSENTIAL INQUIRIES

- Fever, cough, and other symptoms of lower respiratory tract infection.
- Smoking history.
- Nasopharyngeal or GI bleeding.
- Chest radiography and CBC (and, in some cases, INR).

General Considerations

Hemoptysis is the expectoration of blood that originates below the vocal folds. It is commonly classified as trivial, mild, or massive—the latter defined as more than 200–600 mL (about 1–2 cups) in 24 hours. Massive hemoptysis can be usefully defined as any amount that is hemodynamically significant or threatens ventilation. Its in-hospital mortality was 6.5% in one study. The initial goal of management of massive hemoptysis is therapeutic, not diagnostic.

The causes of hemoptysis can be classified anatomically. Blood may arise from the upper airway due to malignant invasion or foreign body; from the airways in COPD, bronchiectasis, bronchial Dieulafoy disease, and bronchogenic carcinoma; from the pulmonary vasculature in LV failure, mitral stenosis, PE, pulmonary arterial hypertension, telangiectasias, arteriovenous malformations, and multiple pulmonary artery aneurysms; from the systemic circulation in intralobar pulmonary sequestration, aortobronchial fistula; or from the pulmonary parenchyma in pneumonia, fungal infections, inhalation of crack cocaine, granulomatosis with polyangiitis, or Takayasu arteritis with pulmonary arteritis. Hemoptysis can be caused by the parasitic diseases paragonimiasis (most common cause worldwide) and human echinococcosis (also called hydatid disease). Diffuse alveolar hemorrhage—manifested by alveolar infiltrates on chest radiography—is due to small vessel bleeding usually caused by autoimmune or hemostatic disorders, or rarely precipitated by hypertensive emergency or anticoagulant therapy. Most cases of hemoptysis presenting in the outpatient setting are due to infection (eg, acute or chronic bronchitis, pneumonia, tuberculosis, infection with *Mycobacterium avium* complex, aspergillosis). Hemoptysis due to lung cancer increases with age, causing up to 20% of cases among older adults. Pulmonary venous hypertension (eg, mitral stenosis, PE) causes hemoptysis in less than 10% of cases. Most cases of hemoptysis that have no visible cause on CT scan or bronchoscopy will resolve within 6 months without treatment, with the notable exception of patients at high risk for lung cancer (patients who smoke cigarettes and are older than 40 years). Iatrogenic hemorrhage may follow transbronchial lung biopsies, anticoagulation, or pulmonary artery rupture due to distal placement of a balloon-tipped catheter. Obstructive sleep apnea with elevated pulmonary arterial pressure may be a risk factor for hemoptysis. Amyloidosis of the lung can cause hemoptysis, as can endometriosis. No cause is identified in up to 15–30% of cases.

Clinical Findings

A. Symptoms

Blood-tinged sputum in the setting of an upper respiratory tract infection in an otherwise healthy, young (age under 40 years) nonsmoker does not warrant an extensive diagnostic evaluation if the hemoptysis subsides with resolution of the infection. However, hemoptysis is frequently a sign of serious disease, especially in patients with a high prior probability of underlying pulmonary pathology. Hemoptysis is the only symptom found to be a specific predictor of lung cancer. It portends a high risk of mortality in COVID-19 infection. There is no value in distinguishing blood-streaked sputum and cough productive of blood during evaluation; the goal of the history is to identify patients at risk for one of the disorders listed earlier. Pertinent features include duration of symptoms, presence of respiratory infection, and past or current tobacco use. Nonpulmonary sources of hemorrhage—from the sinuses or the GI tract—must be excluded.

B. Physical Examination

Elevated pulse, hypotension, and decreased oxygen saturation suggest large-volume hemorrhage that warrants emergent evaluation and stabilization. The nares and oropharynx should be carefully inspected to identify a potential upper airway source of bleeding. Chest and cardiac examination may reveal evidence of HF or mitral stenosis.

C. Diagnostic Studies

Diagnostic evaluation should include a chest radiograph and CBC. Kidney function tests, UA, and coagulation studies are appropriate in specific circumstances. Hematuria that accompanies hemoptysis may be a clue to antibasement membrane antibody disease or vasculitis. Flexible bronchoscopy reveals endobronchial cancer in 3–6% of patients with hemoptysis who have a normal (non-lateralizing) chest radiograph. Nearly all these patients are cigarette smokers over the age of 40, and most will have had symptoms for more than 1 week. High-resolution chest CT scan complements bronchoscopy; it can visualize unsuspected bronchiectasis and arteriovenous malformations and will show central endobronchial cancers in many cases. It is the test of choice for suspected small peripheral malignancies. Helical pulmonary CT angiography is the initial test of choice for evaluating patients with suspected PE, although caution should be taken to avoid large contrast loads in patients with even mild CKD (serum creatinine greater than 2.0 g/dL or rapidly rising creatinine in normal range). Helical CT scanning can be avoided in patients who are at "unlikely" risk for PE using the Wells score or PERC (Pulmonary Embolism Rule-Out Criteria) rule for PE and the sensitive D-dimer test (see Chapter 9). Echocardiography may reveal evidence of HF or mitral stenosis. Multidetector CT angiography is the study of choice to determine the location, etiology, and mechanism of the bleeding.

Treatment

Management of mild hemoptysis consists of identifying and treating the specific cause. Massive hemoptysis is life-threatening. The airway should be protected with endotracheal intubation, ventilation ensured, and effective circulation maintained. If the location of the bleeding site is known, the patient should be placed in the decubitus position with the involved lung dependent. Uncontrollable hemorrhage warrants rigid bronchoscopy and surgical consultation. In stable patients, flexible bronchoscopy may localize the site of bleeding, and angiography can embolize the involved bronchial arteries. Embolization is effective initially in 85% of cases, although rebleeding may occur in

up to 20% of patients during the following year. The anterior spinal artery arises from the bronchial artery in up to 5% of people, and paraplegia may result if it is inadvertently cannulated and embolized.

One double-blind, randomized controlled trial compared treatment with inhalations of tranexamic acid (an antifibrinolytic drug) versus placebo (normal saline) in patients hospitalized with mild hemoptysis (less than 200 mL of expectorated blood per 24 hours). Compared to patients receiving placebo (normal saline), more patients treated with tranexamic acid experienced resolution of hemoptysis within 5 days of admission (96% versus 50%). In addition, mean hospital length of stay was shorter for the tranexamic acid group, and fewer patients required invasive procedures (interventional bronchoscopy, angiographic embolization) to control the hemorrhage. Another randomized study found that compared to the control group, patients given tranexamic acid on admission had significantly lower in-hospital mortality (11.5% versus 9.0%).

When to Refer

- Refer to a pulmonologist when bronchoscopy of the lower respiratory tract is needed.
- Refer to an otolaryngologist when an upper respiratory tract bleeding source is identified.
- Refer to a hematologist when severe coagulopathy complicates management.

When to Admit

- To stabilize bleeding process in patients at risk for or experiencing massive hemoptysis.
- To correct disordered coagulation (using clotting factors or platelets, or both) or to reverse anticoagulation.
- To stabilize gas exchange.

Davidson K et al. Managing massive hemoptysis. Chest. 2020;157:77. [PMID: 31374211]
Kinoshita T et al. Effect of tranexamic acid on mortality in patients with haemoptysis: a nationwide study. Crit Care. 2019;23:347. [PMID: 31694697]

CHEST PAIN

ESSENTIAL INQUIRIES

- Pain onset, character, location/size, duration, periodicity, and exacerbators; shortness of breath.
- Vital signs; chest and cardiac examinations.
- ECG and biomarkers of myocardial necrosis in selected patients.

General Considerations

Chest pain (or chest discomfort) can occur as a result of cardiovascular, pulmonary, pleural, or musculoskeletal disease; esophageal or other GI disorders; herpes zoster; cocaine use; or anxiety states. The frequency and distribution of life-threatening causes of chest pain, such as acute coronary syndrome (ACS), pericarditis, aortic dissection, vasospastic angina, PE, pneumonia, and esophageal perforation, vary substantially between clinical settings.

SLE, rheumatoid arthritis, reduced eGFR, and HIV infection are conditions that confer a strong risk of CAD. Precocious ACS (occurring in patients aged 35 years or younger) may represent acute thrombosis independent of underlying atherosclerotic disease. Risk factors for precocious ACS are obesity, hyperlipidemia, and smoking.

Although ACS presents with a broader range of symptoms in women than men, specific chest pain characteristics of acute MI do not differ in frequency or strength between men and women.

Because PE can present with a wide variety of symptoms, consideration of the diagnosis and rigorous risk factor assessment for venous thromboembolism (VTE) is critical. Classic VTE risk factors include cancer, trauma, recent surgery, prolonged immobilization, pregnancy, oral contraceptives, and family history and prior history of VTE. Other conditions associated with increased risk of PE include HF and COPD. Sickle cell anemia can cause acute chest syndrome. Patients with this syndrome often have chest pain, fever, and cough.

Clinical Findings

A. Symptoms

Myocardial ischemia is usually described as a dull, aching sensation of "pressure," "tightness," "squeezing," or "gas," rather than as sharp or spasmodic. Pain reaching maximum intensity in seconds is uncommon. Ischemic symptoms usually subside within 5–20 minutes but may last longer. Progressive symptoms or symptoms at rest may represent unstable angina. Up to one-third of patients with acute MI do not report chest pain. Chest pain is present in more than 90% of patients having a STEMI who are under age 65 but in only 57% of patients having a STEMI who are over age 85.

Continuous chest pain lasting 24 hours or longer is unlikely due to an acute MI (LR, 0.15). However, chest pain lasting 1 minute or less does not exclude MI (LR, 0.95). When present, pain due to myocardial ischemia is commonly accompanied by a sense of anxiety or uneasiness. The location is usually retrosternal or left precordial. Because the heart lacks somatic innervation, precise localization of pain due to cardiac ischemia is difficult; the pain is commonly referred to the throat, lower jaw, shoulders, inner arms, upper abdomen, or back. Ischemic pain may be precipitated or exacerbated by exertion, cold temperature, meals, stress, or combinations of these factors and is usually relieved by rest. However, many episodes do not conform to these patterns, and a broader range of symptoms of ACS are more common in older adults, women, and persons with diabetes mellitus. Other symptoms that are associated with ACS include shortness of breath; dizziness; a feeling of impending doom; and vagal symptoms, such as nausea and diaphoresis. In older persons, fatigue is a common presenting complaint of ACS.

The presenting symptoms of acute MI in young patients are different in men and women. Women are more likely than men to present with three or more associated symptoms (eg, epigastric symptoms; palpitations; and pain or discomfort in the jaw, neck, arms, or between the shoulder blades; 61.9% for women versus 54.8% for men). In adjusted analyses, women with an acute STEMI were more likely than men to present without chest pain (OR, 1.51). In comparison with men, women were more likely to perceive symptoms as stress/anxiety (20.9% versus 11.8%) but less likely to attribute symptoms to muscle pain (15.4% versus 21.2%).

One analysis found the following clinical features to be associated with acute MI: chest pain that radiates to the left, right, or both arms (LR, 2.3); diaphoresis (LR, 2.0); nausea and vomiting (LR, 1.9); third heart sound (LR, 3.2); systolic blood pressure less than or equal to 80 mm Hg (LR, 3.1); pulmonary crackles (LR, 2.1); any ST-segment elevation greater than or equal to 1 mm (LR, 11.2); any ST depression (LR, 3.2); any Q wave (LR, 3.9); any conduction defect (LR, 2.7); and new conduction defect (LR, 6.3).

A meta-analysis found the clinical findings and risk factors most suggestive of ACS were prior abnormal stress test (specificity, 96%; LR, 3.1), peripheral arterial disease (specificity, 97%; LR, 2.7), and pain radiation to both arms (specificity, 96%; LR, 2.6). The ECG findings associated with ACS were ST-segment depression (specificity, 95%; LR, 5.3) and any evidence of ischemia (specificity, 91%; LR, 3.6). Risk scores derived from both the HEART trial (https://www.mdcalc.com/heart-score-major-cardiac-events) and TIMI trial (https://www.mdcalc.com/timi-risk-score-ua-nstemi#use-cases) performed well in detecting ACS (LR, 13 for HEART score of 7–10, and LR, 6.8 for TIMI score of 5–7).

Hypertrophy of either ventricle or aortic stenosis may also give rise to chest pain with less typical features. Pericarditis produces pain that may be greater when supine than upright and increases with breathing, coughing, or swallowing. Pleuritic chest pain is usually not ischemic, and pain on palpation may indicate a musculoskeletal cause. Aortic dissection classically produces an abrupt onset of tearing pain of great intensity that often radiates to the back; however, this classic presentation occurs in a small proportion of cases. Anterior aortic dissection can also lead to myocardial or cerebrovascular ischemia.

In PE, chest pain is present in about 75% of cases. The chief objective in evaluating patients with suspected PE is to assess the patient's clinical risk for VTE based on medical history and associated symptoms and signs (see above and Chapter 9). Rupture of the thoracic esophagus iatrogenically or secondary to vomiting is another cause of chest pain.

B. Physical Examination

Findings on physical examination can occasionally yield important clues to the underlying cause of chest pain; however, a normal physical examination should never be used as the sole basis for ruling out most diagnoses, particularly ACS and aortic dissection. Vital signs (including pulse oximetry) and cardiopulmonary examination are always the first steps for assessing the urgency and tempo of the subsequent examination and diagnostic workup. Although chest pain that is reproducible or worsened with palpation strongly suggests a musculoskeletal cause, up to 15% of patients with ACS will have reproducible chest wall tenderness. Pointing to the location of the pain with one finger has been shown to be highly correlated with nonischemic chest pain.

Aortic dissection can result in differential blood pressures (greater than 20 mm Hg), pulse amplitude deficits, and new diastolic murmurs. Although hypertension is considered the rule in patients with aortic dissection, systolic blood pressure less than 100 mm Hg is present in up to 25% of patients.

A cardiac friction rub represents pericarditis until proven otherwise. It can best be heard with the patient sitting forward at end-expiration. Tamponade should be excluded in all patients with a clinical diagnosis of pericarditis by assessing pulsus paradoxus (a decrease in systolic blood pressure greater than 10 mm Hg during inspiration) and inspection of jugular venous pulsations. Subcutaneous emphysema is common following cervical esophageal perforation but present in only about one-third of thoracic perforations (ie, those most commonly presenting with chest pain).

The absence of abnormal physical examination findings in patients with suspected PE usually serves to *increase* its likelihood, although a normal physical examination is also compatible with the much more common conditions of panic/anxiety disorder and musculoskeletal disease.

C. Diagnostic Studies

Unless a competing diagnosis can be confirmed, an ECG is warranted in the initial evaluation of most patients with acute chest pain to help exclude ACS. When compared with White patients, Black patients who came to the emergency department with chest pain were less likely to have an ECG ordered (adjusted OR = 0.82). In a study of 11 emergency departments in Italy, 67% of patients with confirmed ACS had new-onset alterations of the ECG (compared with only 6.2% among non-ACS patients). ST-segment elevation is the ECG finding that is the strongest predictor of acute MI; however, up to 20% of patients with ACS can have a normal ECG.

In the emergency department, patients with suspected ACS can be safely removed from cardiac monitoring if they are pain-free at initial physician assessment and have a normal or nonspecific ECG. This decision rule had 100% sensitivity for serious arrhythmia. Clinically stable patients with CVD risk factors, normal ECG, normal cardiac biomarkers, and no alternative diagnoses (such as typical GERD or costochondritis) should be followed up with a timely exercise stress test that includes perfusion imaging. However, more than 25% of patients with stable chest pain referred for noninvasive testing will have normal coronary arteries and no long-term clinical events. The ECG can also provide evidence for alternative diagnoses, such as pericarditis and PE. Chest radiography is often useful in the evaluation of chest pain and is always indicated when cough or shortness of breath accompanies chest pain.

Findings of pneumomediastinum or new pleural effusion are consistent with esophageal perforation. Stress echocardiography is useful in risk stratifying patients with chest pain, even among those with significant obesity.

Diagnostic protocols using a single high-sensitivity troponin assay combined with a standardized clinical assessment are an efficient strategy to rapidly determine whether patients with chest pain are at low risk and may be discharged from the emergency department. A study of the modified HEART score using a single blood draw of either high-sensitivity troponin (3.9 ng/L), high-sensitivity troponin I (0.9 ng/L) or conventional troponin I (0.0 ng/L) at presentation had a sensitivity of 100% for 30-day major adverse cardiac events. Point-of-care troponin testing during ambulance transport to the emergency department has been found to have good specificity and positive predictive value (99.2% and 85.7%) but poor sensitivity (26.5%).

Six established risk scores are (1) the modified Goldman Risk Score, (2) TIMI Risk Score, (3) Global Registry of Acute Cardiac Events Risk Score, (4) HEART Risk Score, (5) Vancouver Chest Pain Rule, and (6) the European Society of Cardiology (ESC) 0/1-h algorithm. A study comparing these risk scores (not including the ESC algorithm) for predicting acute MI within 30 days reported a sensitivity of 98% (which correlates with a negative predictive value of greater than or equal to 99.5%). Patients eligible for discharge (about 30%) were those with a TIMI score of less than or equal to 1, modified Goldman score of less than or equal to 1 with normal high-sensitivity troponin T, TIMI score of 0, or HEART score of less than or equal to 3 with normal high-sensitivity troponin I. In Black patients with average cardiovascular risk, HEART score is a better predictive tool for 6-week major adverse cardiac events when compared to TIMI score. Six-week major adverse cardiac events among patients with a low-risk HEART score (0–3) was 0.9–1.7%. The HEART score performs poorly in stratifying risk from cocaine-associated chest pain.

The Emergency Department Assessment of Chest Pain Score identified more patients as low-risk compared to the Heart Pathway (58.1% to 38.4%), but major adverse cardiac events occurred in 0.4% of Heart Pathway patients compared to 1.0% of the Emergency Department Assessment of Chest Pain Score identified patients.

While some studies of high-sensitivity cardiac troponin suggest that it may be the best cardiac biomarker, it may not outperform conventional troponin assays if an appropriate cutoff is used.

Patients who arrive at the emergency department with chest pain of intermediate or high probability for ACS without electrocardiographic or biomarker evidence of an MI can be safely discharged from an observation unit after stress cardiac MRI. Sixty-four–slice coronary CT angiography is an alternative to stress testing in the emergency department for detecting ACS among patients with normal or nonspecific ECG and normal biomarkers. A meta-analysis of nine studies found CT angiography had an estimated sensitivity of 95% for ACS and specificity of 87%, yielding an a negative LR of 0.06 and a positive LR of 7.4.

Functional testing appears to be the best initial noninvasive test in symptomatic patients with suspected CAD. CT-derived fractional flow reserve in acute chest pain has higher specificity for anatomic and physiologic assessment of coronary artery stenosis compared with coronary CT angiography. Coronary CT angiography applied early in the evaluation of suspected ACS does not identify more patients with significant CAD requiring coronary revascularization, shorten hospital stay, or allow for more direct discharge from the emergency department compared to high-sensitivity troponins. CT angiography is an option for patients who do not have access to functional testing.

A minimal-risk model developed by the PROMISE investigators includes 10 clinical variables that correlate with normal coronary CT angiography results and no clinical events: (1) younger age; (2) female sex; (3) racial or ethnic minority; (4–6) no history of hypertension, diabetes, or dyslipidemia; (7) no family history of premature CAD; (8) never smoking; (9) symptoms unrelated to physical or mental stress; and (10) higher HDL cholesterol level. In the PROMISE trial, women had higher rates of normal noninvasive testing compared with men, but women with abnormalities on such testing were less likely to be referred for catheterization or to receive statin therapy.

In the evaluation of PE, diagnostic test decisions and results must be interpreted in the context of the clinical likelihood of VTE. A negative D-dimer test is helpful for excluding PE in patients with low clinical probability of VTE (3-month incidence = 0.5%); however, the 3-month risk of VTE among patients with intermediate and high risk of VTE is sufficiently high in the setting of a negative D-dimer test (3.5% and 21.4%, respectively) to warrant further imaging given the life-threatening nature of this condition if left untreated. CT angiography has replaced ventilation-perfusion scanning as the preferred initial diagnostic test, having approximately 90–95% sensitivity and 95% specificity for detecting PE (compared with pulmonary angiography). However, for patients with high clinical probability of VTE, lower extremity ultrasound or pulmonary angiogram may be indicated even with a normal helical CT.

Panic disorder is a common cause of chest pain, accounting for up to 25% of cases that present to emergency departments and a higher proportion of cases presenting in primary care office practices. Features that correlate with an increased likelihood of panic disorder include absence of CAD, atypical quality of chest pain, female sex, younger age, and a high level of self-reported anxiety. Depression is associated with recurrent chest pain with or without CAD (OR, 2.11).

Treatment

Treatment of chest pain should be guided by the underlying etiology. The term "noncardiac chest pain" is used when a diagnosis remains elusive after patients have undergone an extensive workup. Almost half of patients with noncardiac chest pain reported symptom improvement with high-dose PPI therapy. Relief of constipation may be therapeutic in PPI refractory noncardiac chest pain. A meta-analysis of 15 trials suggested modest to moderate benefit for psychological (especially cognitive-behavioral) interventions. It is unclear whether tricyclic

or SSRI antidepressants have benefit in noncardiac chest pain. Hypnotherapy may offer some benefit.

When to Refer

- Refer patients with poorly controlled, noncardiac chest pain to a pain specialist.
- Refer patients with angina that is poorly controlled using maximal medical therapy to a cardiologist.
- Refer patients with sickle cell anemia to a hematologist.

When to Admit

- Failure to adequately exclude life-threatening causes of chest pain, particularly MI, dissecting aortic aneurysm, PE, and esophageal rupture.
- Patients with high-risk of complications from PE, or when PE is likely despite negative spiral CT.
- TIMI score of 1 or more, HEART score greater than 3, abnormal ECG, and abnormal 0- and 2-hour troponin tests.
- Pain control for rib fracture that impairs gas exchange.

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PALPITATIONS

ESSENTIAL INQUIRIES

- Forceful, rapid, or irregular beating of the heart.
- Rate, duration, and degree of regularity of heartbeat; age at first episode.
- Factors that precipitate or terminate episodes.
- Light-headedness or syncope; neck pounding.
- Chest pain; history of MI or structural heart disease.

General Considerations

Palpitations are defined as an unpleasant awareness of the forceful, rapid, or irregular beating of the heart. They are the primary symptom for approximately 16% of patients presenting to an outpatient clinic with a cardiac complaint. In an observational cohort study of palpitations at an outpatient cardiac unit, cardiac arrhythmias were the cause of palpitations in 81% of cases. Palpitations represent 5.8 of every 1000 emergency department visits, with an admission rate of 24.6%. While palpitations are usually benign, they are occasionally the symptom of a life-threatening arrhythmia. To avoid missing a dangerous cause of the patient's symptom, clinicians sometimes pursue expensive and invasive testing when a conservative diagnostic evaluation is often sufficient. The converse is also true. Table 2–3 lists history, physical examination, and ECG findings suggesting a cardiovascular cause for the palpitations.

When assessing a patient with palpitations in an urgent care setting, the clinician must ascertain whether the symptoms represent (1) a significant CVD, (2) a cardiac manifestation of a systemic disease such as thyrotoxicosis, (3) an arrhythmia that is minor and transient, or (4) a benign somatic symptom that is amplified by the patient's underlying psychological state.

Etiology

Patients with palpitations who seek medical attention in an emergency department instead of a medical clinic are more likely to have a cardiac cause (47% versus 21%), whereas psychogenic causes are more common among those who seek attention in office practices (45% versus 27%). In a study of patients who went to a university medical clinic with the chief complaint of palpitations, causes were cardiac in 43%, psychogenic in 31%, and miscellaneous in 10%.

Cardiac arrhythmias that can result in symptoms of palpitations include sinus bradycardia; atrial fibrillation or flutter; sinus, supraventricular, and ventricular tachycardia; premature ventricular and atrial contractions; sick sinus syndrome; and advanced atrioventricular block.

Cardiac structural causes of palpitations include valvular heart diseases, such as aortic regurgitation or stenosis, atrial or ventricular septal defect, cardiomyopathy, congenital heart disease, pericarditis, arrhythmogenic RV cardiomyopathy, and atrial myxoma. Mitral valve prolapse is not associated with arrhythmic events, but ventricular arrhythmias are frequent in mitral annulus disjunction.

Pericardial or myocardial infection with SARS-CoV-2, tuberculosis, and *Trypanosoma cruzi* (Chagas disease) can cause palpitations.

The most common psychogenic causes of palpitations are anxiety and panic disorder. The release of catecholamines during a significant stress or panic attack can trigger an arrhythmia. Asking a single question, "Have you experienced brief periods, for seconds or minutes, of an overwhelming panic or terror that was accompanied by racing heartbeats, shortness of breath, or dizziness?" can help identify patients with panic disorder.

Other causes of palpitations include fever, dehydration, hypoglycemia, anemia, thyrotoxicosis, mastocytosis, and

pheochromocytoma. Drugs (such as cocaine, alcohol, caffeine, pseudoephedrine, cannabis, and illicit ephedra), prescription medications (including digoxin, amitriptyline, erythromycin, methylphenidate) as well as other drugs that prolong the QT interval, class 1 antiarrhythmics, dihydropyridine calcium channel blockers, phenothiazines, theophylline, and beta-agonists can precipitate palpitations.

Clinical Findings

A. Symptoms

Guiding the patient through a careful description of their palpitations may indicate a mechanism and narrow the differential diagnosis. Pertinent questions include the age at first episode; precipitants; and rate, duration, and degree of regularity of the heartbeat during the subjective palpitations. Palpitations lasting less than 5 minutes and a family history of panic disorder reduce the likelihood of an arrhythmic cause (LR+ = 0.38 and LR+ = 0.26, respectively). To better understand the symptom, the examiner can ask the patient to "tap out" the rhythm with his or her fingers. The circumstances associated with onset and termination can also be helpful in determining the cause. Palpitations that start and stop abruptly suggest supraventricular or ventricular tachycardias. Termination of palpitations using vagal maneuvers (eg, Valsalva maneuver) suggests supraventricular tachycardia.

Three common descriptions of palpitations are (1) "flip-flopping" (or "stop and start"), often caused by premature contraction of the atrium or ventricle, with the perceived "stop" from the pause following the contraction, and the "start" from the subsequent forceful contraction; (2) rapid "fluttering in the chest," with regular "fluttering" suggesting supraventricular or ventricular arrhythmias (including sinus tachycardia) and irregular "fluttering" suggesting atrial fibrillation, atrial flutter, or tachycardia with variable block; and (3) "pounding in the neck" or neck pulsations, often due to "cannon" A waves in the jugular venous pulsations that occur when the right atrium contracts against a closed tricuspid valve.

Palpitations associated with chest pain suggest ischemic heart disease, or if the chest pain is relieved by leaning forward, pericardial disease. Palpitations associated with light-headedness, presyncope, or syncope suggest hypotension and may signify a life-threatening cardiac arrhythmia. Palpitations that occur regularly with exertion suggest a rate-dependent bypass tract or hypertrophic cardiomyopathy as well as silent ischemia. If a benign etiology cannot be ascertained at the initial visit, then ambulatory monitoring or prolonged cardiac monitoring in the hospital might be warranted.

Noncardiac symptoms should also be elicited since the palpitations may be caused by a normal heart responding to a metabolic or inflammatory condition. Weight loss suggests hyperthyroidism. Palpitations can be precipitated by vomiting or diarrhea causing electrolyte disorders and hypovolemia. Hyperventilation, hand tingling, and nervousness are common when anxiety or panic disorder is the cause of the palpitations. Palpitations associated with flushing, episodic hypertension, headaches, anxiety, and diaphoresis may be caused by a pheochromocytoma or paraganglioma.

A family history of palpitations or sudden death suggests an inherited etiology such as long QT syndrome or Brugada syndrome. Chagas disease may cause palpitations and acute myocarditis. Younger patients should be asked about consumption of "energy drinks." Finally, dual use of cigarettes and e-cigarettes may cause palpitations.

B. Physical Examination

Careful cardiovascular examination can find abnormalities that can increase the likelihood of specific cardiac arrhythmias. The midsystolic click of mitral valve prolapse can suggest the diagnosis of a supraventricular arrhythmia. The harsh holosystolic murmur of hypertrophic cardiomyopathy, which occurs along the left sternal border and increases with the Valsalva maneuver, suggests atrial fibrillation or ventricular tachycardia. A crescendo mid-diastolic murmur may be caused by an atrial myxoma. The presence of dilated cardiomyopathy, suggested on examination by a displaced and enlarged cardiac point-of-maximal impulse, increases the likelihood of ventricular tachycardia and atrial fibrillation. In patients with chronic atrial fibrillation, in-office exercise (eg, a brisk walk in the hallway) may reveal an intermittent accelerated ventricular response. The clinician should also look for signs of hyperthyroidism (eg, tremulousness, brisk deep tendon reflexes, or fine hand tremor) or signs of stimulant drug use (eg, dilated pupils or skin or nasal septal perforations). Visible neck pulsations (LR+, 2.68) in association with palpitations increase the likelihood of atrioventricular nodal reentry tachycardia.

C. Diagnostic Studies

1. ECG—A 12-lead ECG should be performed on all patients reporting palpitations, although in most instances, a specific arrhythmia will not be detected. Evidence of prior MI on ECG (eg, Q waves) increases the patient's risk of nonsustained or sustained ventricular tachycardia. Ventricular preexcitation (Wolff-Parkinson-White syndrome) is suggested by a short PR interval (less than 0.20 ms) and delta waves (upsloping PR segments). The presence of left atrial enlargement as suggested by a terminal P-wave force in V1 more negative than 0.04 msec and notching in lead II reflects an increased risk of atrial fibrillation. A prolonged QT interval and abnormal T-wave morphology suggest the long QT syndrome, and an increased risk of ventricular tachycardia.

2. Monitoring devices—For high-risk patients (Table 2–3), further diagnostic studies are warranted. A stepwise approach has been suggested—starting with ambulatory monitoring devices (ambulatory ECG monitoring if the palpitations are expected to occur within the subsequent 72-hour period, event monitoring if less frequent). An implantable loop recorder can be used for extended monitoring if clinical suspicion is high, especially if there is syncope. A single-lead, lightweight, continuously recording ambulatory adhesive patch monitor (Zio Patch)

Table 2–3. Palpitations: Patients at high risk for a cardiovascular cause.

Historical risk factors
Family history of significant arrhythmias
Personal or family history of syncope or resuscitated sudden death
History of MI
Palpitations that occur during sleep
Anatomic abnormalities
Structural heart disease such as dilated or hypertrophic cardiomyopathies
Valvular disease (stenotic or regurgitant)
ECG findings
Long QT syndrome
Bradycardia
Second- or third-degree heart block
Sustained ventricular arrhythmias

worn for 14–21 days increases diagnostic yield while reducing cost of diagnosis in patients with recurrent unexplained palpitations. Inpatient continuous monitoring is indicated if serious arrhythmias are strongly suspected despite normal findings on the ambulatory monitoring; invasive electrophysiologic testing should be done if the ambulatory or inpatient monitor records a worrisome arrhythmia.

In patients with a prior MI, ambulatory cardiac monitoring or signal-averaged ECG is an appropriate next step to help exclude ventricular tachycardia. ECG exercise testing is appropriate in patients with suspected CAD and in patients who have palpitations with physical exertion. Echocardiography is useful when physical examination or ECG suggests structural abnormalities or decreased ventricular function.

Treatment

After ambulatory monitoring, most patients with palpitations are found to have benign atrial or ventricular ectopy or nonsustained ventricular tachycardia. In patients with structurally normal hearts, these arrhythmias are not associated with adverse outcomes. Abstention from caffeine and tobacco may help. Often, reassurance suffices. If not, or in very symptomatic patients, a trial of a beta-blocker may be prescribed. A three-session course of cognitive-behavioral therapy that includes some physical activity has proven effective for patients with benign palpitations with or without chest pain. For treatment of specific atrial or ventricular arrhythmias, see Chapter 10.

When to Refer

- For electrophysiologic studies.
- For advice regarding treatment of atrial or ventricular arrhythmias.

When to Admit

- Palpitations associated with syncope or near-syncope, particularly when the patient is aged 75 years or older and has an abnormal ECG, hematocrit less than 30%, shortness of breath, respiratory rate higher than 24/min, or a history of HF.
- Patients with risk factors for a serious arrhythmia.

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LOWER EXTREMITY EDEMA

ESSENTIAL INQUIRIES

- History of VTE.
- Symmetry of swelling.
- Pain.
- Change with dependence.
- Skin findings: hyperpigmentation, stasis dermatitis, lipodermatosclerosis, atrophie blanche, ulceration.

General Considerations

Acute and chronic lower extremity edema present important diagnostic and treatment challenges. **Chronic venous insufficiency** is by far the most common cause, affecting up to 2% of the population, and the incidence of venous insufficiency has not changed over the past 25 years. Venous insufficiency is a common complication of DVT; however, only a small number of patients with chronic venous insufficiency report a history of this disorder. Venous ulceration commonly affects patients with chronic venous insufficiency, and its management is labor-intensive and expensive. Normal lower extremity venous pressure (in the erect position: 80 mm Hg in deep veins, 20–30 mm Hg in superficial veins) and cephalad venous blood flow require competent bicuspid venous valves, effective muscle contractions, normal ankle range of motion, and normal respirations. When one or more of these components fail, venous hypertension may result. Chronic edema increases the risk of cellulitis, with risk increasing as the stage of edema increases.

Clinical Findings

A. Symptoms and Signs

1. Unilateral lower extremity edema—Among common causes of unilateral lower extremity swelling, DVT is the most life-threatening. Clues suggesting DVT include a history of cancer, recent limb immobilization, or confinement to bed for at least 3 days following major surgery within the

Table 2–4. Risk stratification of adults referred for ultrasound to rule out DVT.

Step 1:		
Score 1 point for each		
Untreated malignancy		
Paralysis, paresis, or recent plaster immobilization		
Recently bedridden for > 3 days due to major surgery within 4 weeks		
Localized tenderness along distribution of deep venous system		
Entire leg swelling		
Swelling of one calf > 3 cm more than the other (measured 10 cm below tibial tuberosity)		
Ipsilateral pitting edema		
Collateral superficial (nonvaricose) veins		
Previously documented DVT		
Step 2:		
Subtract 2 points if alternative diagnosis has equal or greater likelihood than DVT		
Step 3:		
Obtain sensitive D-dimer for score ≥ 0		
Score	**D-Dimer Positive[1]**	**D-Dimer Negative**
0–1	Obtain ultrasound	Ultrasound not required
≥ 2	Obtain ultrasound	

[1]"Positive" is above local laboratory threshold based on specific test and patient age.

past month (Table 2–4). Adults with varicose veins have a significantly increased risk of DVT. Lower extremity swelling and inflammation in a limb recently affected by DVT could represent anticoagulation failure and thrombus recurrence but more often are caused by **postphlebitic syndrome** with valvular incompetence. Other causes of a painful, swollen calf include cellulitis, musculoskeletal disorders (Baker cyst rupture ["pseudothrombophlebitis"]), gastrocnemius tear or rupture, calf strain or trauma, and left common iliac vein compression (May-Thurner syndrome), as well as other sites of nonthrombotic venous outflow obstruction, such as the inguinal ligament, iliac bifurcation, and popliteal fossa.

2. Bilateral lower extremity edema—Bilateral involvement and significant improvement upon awakening favor systemic causes (eg, venous insufficiency) and can be presenting symptoms of volume overload (HF, cirrhosis, kidney disease [eg, nephrotic syndrome]). The most frequent symptom of chronic venous insufficiency is the sensation of "heavy legs," followed by itching. Chronic exposure to elevated venous pressure accounts for the brawny, fibrotic skin changes observed in patients with chronic venous insufficiency as well as the predisposition toward skin ulceration, particularly in the medial malleolar area. Pain, particularly if severe, is uncommon in uncomplicated venous insufficiency.

Lower extremity swelling is a familiar complication of therapy with calcium channel blockers (particularly felodipine and amlodipine), pioglitazone, gabapentin, and minoxidil. Prolonged airline flights (longer than 10 hours) are associated with edema even in the absence of DVT.

B. Physical Examination

Physical examination should include assessment of the heart, lungs, and abdomen for evidence of pulmonary hypertension (primary or secondary to chronic lung disease), HF, or cirrhosis. The skin findings related to chronic venous insufficiency depend on the severity and chronicity of the disease, ranging from hyperpigmentation and stasis dermatitis to abnormalities highly specific for chronic venous insufficiency: lipodermatosclerosis (thick, brawny skin; in advanced cases, the lower leg resembles an inverted champagne bottle) and atrophie blanche (small, depigmented macules within areas of heavy pigmentation). The size of both calves should be measured 10 cm below the tibial tuberosity and pitting and tenderness elicited. Swelling of the entire leg or of one leg 3 cm more than the other suggests deep venous obstruction. The left calf is normally slightly larger than the right as a result of the left common iliac vein coursing under the aorta.

A shallow, large, modestly painful ulcer located over the medial malleolus is a hallmark of chronic venous insufficiency, whereas small, deep, and more painful ulcers are more apt to be due to arterial insufficiency, vasculitis, or infection. Diabetic vascular ulcers, however, may be painless. When an ulcer is on the foot or above the mid-calf, causes other than venous insufficiency should be considered.

The physical examination is usually inadequate to distinguish lymphedema from venous insufficiency. Only the Kaposi-Stemmer sign (the inability to pinch or pick up a fold of skin at the base of the second toe because of its thickness) was a significant predictor of lymphedema (OR, 7.9; $P = 0.02$).

C. Diagnostic Studies

Patients without an obvious cause of acute unilateral lower extremity swelling (eg, calf strain) should have an ultrasound performed, since DVT is difficult to exclude on clinical grounds. A prediction rule allows a clinician to exclude a lower extremity DVT in patients without an ultrasound if the patient has low pretest probability for DVT and a negative sensitive D-dimer test (the "Wells prediction rule") (https://www.mdcalc.com/wells-criteria-pulmonary-embolism) (Chapter 9).

The diagnostic study of choice to detect chronic venous insufficiency due venous incompetence is duplex ultrasonography. Assessment of the ankle-brachial pressure index is important in the management of chronic venous insufficiency since peripheral arterial disease may be exacerbated by compression therapy. Caution is required in interpreting the results of ankle-brachial pressure index in older patients and diabetic patients due to the decreased compressibility of their arteries. A urine dipstick test that is strongly positive for protein can suggest nephrotic

syndrome, and a serum creatinine can help estimate kidney function. Measuring serum albumin can be considered to further evaluate suspected nephrotic syndrome or when chronic liver disease is suspected. Lymphoscintigraphy can be used to confirm a clinical suspicion of lymphedema.

Treatment

See relevant chapters for treatment of edema in patients with HF (Chapter 10), nephrosis (Chapter 22), cirrhosis (Chapter 16), and lymphedema and venous stasis ulcers (Chapter 12). Edema resulting from calcium channel blocker therapy responds to concomitant therapy with ACE inhibitors or ARBs.

In patients with chronic venous insufficiency without a comorbid volume overload state (eg, HF), it is best to avoid diuretic therapy. These patients have relatively decreased intravascular volume, and administration of diuretics may first enhance sodium retention through increased secretion of renin and angiotensin and then result in AKI and oliguria. Instead, the most effective treatment involves (1) leg elevation, above the level of the heart, for 30 minutes three to four times daily, and during sleep; (2) compression therapy; and (3) ambulatory exercise to increase venous return through calf muscle contractions.

A wide variety of stockings and devices are effective in decreasing swelling and preventing ulcer formation and reducing the risk of cellulitis. They should be put on with awakening before hydrostatic forces result in edema. To control mild edema, 20–30 mm Hg compression is usually sufficient, whereas 30–40 mm Hg compression is usually required to control moderate to severe edema associated with ulcer formation. To maintain improvement, consider switching from an elastic stocking to one made of inelastic grosgrain material. Patients with decreased ankle-brachial pressure index should be managed in concert with a vascular surgeon. Compression stockings (12–18 mm Hg at the ankle) are effective in preventing edema and asymptomatic thrombosis associated with long airline flights in low- to medium-risk persons, and compression therapy decreases recurrence of cellulitis among patients with chronic venous insufficiency. Support stockings are recommended for pregnant women during air travel. For lymphedema, bandaging systems applied twice weekly can be effective. Multi-component compression bandaging may offer additional benefit. Short-term manual lymphatic drainage treatment may improve chronic venous insufficiency severity, symptoms, and quality of life. For patients with reduced mobility and leg edema, intermittent pneumatic compression treatment can reduce edema and improve ankle range of motion.

Liposuction, suction-assisted lipectomy, and subcutaneous drainage may have treatment benefit if conservative measures fail in treatment of lymphedema.

When to Refer

- Refer patients with chronic lower extremity ulcerations to wound care specialist.
- Refer patients with nephrotic syndrome to a nephrologist.
- Refer patients with coexisting severe arterial insufficiency (claudication) that would complicate treatment with compression stockings to a vascular surgeon.

When to Admit

- Pending definitive diagnosis in patients at high risk for DVT despite normal lower extremity ultrasound.
- Severe, acute swelling raising concern for an impending compartment syndrome.
- Severe edema that impairs ability to ambulate or perform activities of daily living.

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FEVER & HYPERTHERMIA

ESSENTIAL INQUIRIES

- Age; injection substance use.
- Localizing symptoms; weight loss; joint pain.
- Immunosuppression or neutropenia; history of cancer, risk of COVID-19.
- Medications.
- Travel.

General Considerations

The average normal oral body temperature taken in midmorning is 36.7°C (range 36–37.4°C). This range includes a mean and 2 standard deviations, thus encompassing 95% of a normal population (normal diurnal temperature variation is 0.5–1°C).

The normal rectal or vaginal temperature is 0.5°C higher than the oral temperature, and the axillary temperature is 0.5°C lower. However, a normal body temperature based on a peripheral thermometer (tympanic membrane, temporal artery, axillary, oral) does not always exclude the presence of a fever. To exclude a fever, a rectal temperature is more reliable than an oral temperature (particularly in patients who breathe through their mouth, who are tachypneic, or who are in an ICU setting where a rectal temperature probe can be placed to detect fever).

Fever is a regulated rise to a new "set point" of body temperature in the hypothalamus induced by pyrogenic cytokines. These cytokines include interleukin-1 (IL-1), tumor necrosis factor, interferon-gamma, and interleukin-6 (IL-6). The elevation in temperature results from either increased heat production (eg, shivering) or decreased heat loss (eg, peripheral vasoconstriction). **Hyperthermia**—not mediated by cytokines—occurs when body metabolic heat production (as in thyroid storm) or

environmental heat load exceeds normal heat loss capacity or when there is impaired heat loss (eg, heat stroke). *Body temperature in cytokine-induced fever seldom exceeds 41.1°C unless there is structural damage to hypothalamic regulatory centers; body temperature in hyperthermia may rise to levels (more than 41.1°C) capable of producing irreversible protein denaturation and resultant brain damage; no diurnal variation is observed.*

Clinical Findings

A. Fever

Fever as a symptom provides important information about the presence of illness—particularly infections—and about changes in the clinical status of the patient. Fever may be more predictive of bacteremia in elderly patients. The fever pattern, however, is of marginal value for most specific diagnoses except for the relapsing fever of malaria, borreliosis, and occasional cases of lymphoma, especially Hodgkin disease. Furthermore, the degree of temperature elevation does not necessarily correspond to the severity of the illness. Fever with rash and eosinophilia defines the **d**rug **r**eaction with **e**osinophilia and **s**ystemic **s**ymptoms (DRESS) syndrome.

In general, the febrile response tends to be greater in children than in adults. In older persons, neonates, and persons receiving certain medications (eg, NSAIDs, corticosteroids), rather than a fever, a normal temperature or even hypothermia may be observed. Markedly elevated body temperature may result in profound metabolic disturbances. High temperature during the first trimester of pregnancy may cause birth defects, such as anencephaly. Fever increases insulin requirements and alters the metabolism and disposition of drugs used for the treatment of the diverse diseases associated with fever.

The source of fever varies by population and setting. In a study of 92 patients who underwent shoulder arthroplasty and developed fever, an infectious cause was found in only 6 patients. In the neurologic ICU, fever can occur directly from brain injury (called "central fever"). One model predicted "central fever" with 90% probability if a patient met all of the following criteria: (1) less than 72 hours of neurologic ICU admission; (2) presence of subarachnoid hemorrhage, intraventricular hemorrhage, or brain tumor; (3) absence of infiltrate on chest radiograph; and (4) negative cultures. Procalcitonin and CRP may have some utility in differentiating infectious and central fever in the ICU.

Fever may also be more common in patients with other forms of trauma. In a study enrolling 268 patients, including patients with multiple injuries (n = 59), isolated head injuries (n = 97), isolated body injuries (n = 100), and minor trauma (n = 12), the incidence of fever was similar in all groups irrespective of injury (11–24%). In all groups, there was a significant association between the presence of early fever and death in the hospital (6–18% versus 0–3%), as well as longer median ICU stays (3–7 days versus 2–3 days). Spinal cord injury may cause fever by the loss of supraspinal control of the sympathetic nervous system and defective thermoregulation due to loss of sensation.

Among pregnant women, the prevalence of intrapartum fever of 38°C or greater in pregnancies of 36 weeks' gestation or more is 6.8% (or 1 in 15 women in labor), but the neonatal sepsis rate among affected mothers is 0.24% (or less than 1 in 400 babies). This finding calls into question the need for universal laboratory work, cultures, and antibiotic treatment pending culture results for this newborn population.

Contrary to classical teaching, postoperative atelectasis probably does not cause fever. Febrile nonhemolytic transfusion reaction is common, occurring in about 1% of transfusion episodes, and is mediated by proinflammatory cytokines elaborated by donor leukocytes during storage.

B. Hyperthermia

Hyperthermia—not mediated by cytokines—occurs when body metabolic heat production (as in thyroid storm) or environmental heat load exceeds normal heat loss capacity or when there is impaired heat loss (eg, heat stroke).

Malignant catatonia is a disorder consisting of catatonic symptoms, hyperthermia, autonomic instability, and altered mental status.

Neuroleptic malignant syndrome, a variant of malignant catatonia, is a rare and potentially lethal idiosyncratic reaction to neuroleptic medications, particularly haloperidol and fluphenazine; however, it has also been reported with the atypical neuroleptics (such as olanzapine or risperidone) (see Chapter 25). **Serotonin syndrome** resembles neuroleptic malignant syndrome but occurs within hours of ingestion of agents that increase levels of serotonin in the CNS, including SSRIs, MAOIs, tricyclic antidepressants, meperidine, dextromethorphan, bromocriptine, tramadol, lithium, and psychostimulants (such as cocaine, methamphetamine, and MDMA) (see Chapter 38).

Clonus and hyperreflexia are more common in serotonin syndrome, whereas "lead pipe" rigidity is more common in neuroleptic malignant syndrome. Neuroleptic malignant and serotonin syndromes share common clinical and pathophysiologic features with **malignant hyperthermia of anesthesia** (see Chapter 38).

C. Fever of Undetermined Origin

See Fever of Unknown Origin, Chapter 30.

Treatment

Most fever is well tolerated. When the temperature is less than 40°C, symptomatic treatment only is required. The treatment of fever with antipyretics does not appear to affect mortality of critically ill patients or affect the number of ICU-free days. A temperature greater than 41°C is likely to be hyperthermia rather than cytokine-mediated fever, and *emergent management is indicated.* (See Heat Stroke, Chapter 37.)

A. General Measures for Removal of Heat

Regardless of the cause of the fever, alcohol sponges, cold sponges, ice bags, ice-water enemas, and ice baths will

lower body temperature (see Chapter 37). They are more useful in hyperthermia since patients with cytokine-related fever will attempt to override these therapies.

B. Pharmacologic Treatment of Fever

1. Antipyretic drugs—Antipyretic therapy is not needed except for patients with marginal hemodynamic status. Early administration of acetaminophen to treat fever due to probable infection did not affect the number of ICU-free days. Aspirin or acetaminophen, 325–650 mg every 4 hours, is effective in reducing fever. These drugs are best administered around the clock, rather than as needed, since "as needed" dosing results in periodic chills and sweats due to fluctuations in temperature caused by varying levels of drug.

2. Prophylactic antimicrobial therapy—Antibacterial and antifungal prophylactic regimens are recommended only for patients expected to have less than 100 neutrophils/mcL for more than 7 days, unless other factors increase risks for complications or mortality.

3. Empiric antimicrobial therapy—Empiric antibiotic therapy is sometimes warranted. Even before infection can be documented, prompt broad-spectrum antimicrobials are indicated for febrile patients who have hemodynamic instability, severe neutropenia (neutrophils less than 500/mcL [0.5×10^9/L]), asplenia (surgical or from sickle cell disease), or immunosuppression (from HIV infection [see Chapter 31] or from medications such as systemic corticosteroids, azathioprine, cyclosporine) (Tables 30–4 and 30–5). Febrile neutropenic patients should receive initial doses of empiric antibacterial therapy within an hour of triage and should either be monitored for at least 4 hours to determine suitability for outpatient management or be admitted to the hospital (see Infections in the Immunocompromised Patient, Chapter 30). It is standard to admit patients to the hospital with febrile neutropenic episodes, although carefully selected patients may be managed as outpatients after systematic assessment beginning with a validated risk index (eg, Multinational Association for Supportive Care in Cancer [MASCC] score or Talcott rules). In the MASCC index calculation, low-risk factors include the following: age under 60 years (2 points), burden of illness (5 points for no or mild symptoms and 3 points for moderate symptoms), outpatient status (3 points), solid tumor or hematologic malignancy with no previous fungal infection (4 points), no COPD (4 points), no dehydration requiring parenteral fluids (3 points), and systolic blood pressure greater than 90 mm Hg (5 points). Patients with MASCC scores of 21 or higher or in Talcott group 4 (presentation as an outpatient without significant comorbidity or uncontrolled cancer), and without other risk factors, can be managed safely as outpatients.

The carefully selected outpatients determined to be at low risk by MASCC score (particularly in combination with a normal serum CRP level) or by Talcott rules can be managed with an oral fluoroquinolone plus amoxicillin/clavulanate (or clindamycin, if penicillin allergic), unless fluoroquinolone prophylaxis was used before fever developed. For treatment of fever during neutropenia following chemotherapy, outpatient parenteral antimicrobial therapy can be provided effectively and safely in low-risk patients with a single agent such as cefepime, piperacillin/tazobactam, imipenem, meropenem, or doripenem. High-risk patients should be referred for inpatient management with combination parenteral antimicrobial therapy based on specific risk factors such as pneumonia-causing pathogens or central line–associated bloodstream infections (see Infections in the Immunocompromised Patient and Table 30–5 in Chapter 30 and see Infections in Chapter 39).

If a fungal infection is suspected in patients with prolonged fever and neutropenia, fluconazole is an equally effective but less toxic alternative to amphotericin B.

C. Treatment of Hyperthermia

Discontinuation of the offending agent is mandatory. Treatment of neuroleptic malignant syndrome includes dantrolene in combination with bromocriptine or levodopa (see Chapter 25). Treatment of serotonin syndrome includes administration of a central serotonin receptor antagonist—cyproheptadine or chlorpromazine—alone or in combination with a benzodiazepine (see Chapter 38). In patients for whom it is difficult to distinguish which syndrome is present, treatment with a benzodiazepine may be the safest therapeutic option.

When to Admit

- Presence of additional vital sign abnormalities or evidence of end-organ dysfunction in clinical cases when early sepsis is suspected.
- Febrile neutropenic patients at high risk for clinical decompensation.
- For measures to control a temperature higher than 41°C or when fever is associated with seizure or other mental status changes.
- Heat stroke (see Chapter 37).
- Malignant catatonia; neuroleptic malignant syndrome; serotonin syndrome; malignant hyperthermia of anesthesia.

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INVOLUNTARY WEIGHT LOSS

ESSENTIAL INQUIRIES

- Age; caloric intake; secondary confirmation (eg, changes in clothing size).
- Fever; change in bowel habits.
- Substance use.
- Age-appropriate cancer screening history.

General Considerations

Body weight is determined by a person's caloric intake, absorptive capacity, metabolic rate, and energy losses. Body weight normally peaks by the fifth or sixth decade and then gradually declines at a rate of 1–2 kg per decade. In NHANES II, a national survey of community-dwelling elders (aged 50–80 years), recent involuntary weight loss (more than 5% usual body weight) was reported by 7% of respondents, and this was associated with a 24% higher mortality. In postmenopausal women, unintentional weight loss was associated with increased rates of hip and vertebral fractures.

Etiology

Involuntary weight loss is regarded as clinically significant when it exceeds 5% or more of usual body weight over a 6- to 12-month period. It often indicates serious physical or psychological illness. Physical causes are usually evident during the initial evaluation. The most common causes are cancer (about 30%), GI disorders (about 15%), and dementia or depression (about 15%). Nearly half of patients with Parkinson disease have weight loss associated with disease progression. When an adequately nourished–appearing patient complains of weight loss, inquiry should be made about exact weight changes (with approximate dates) and about changes in clothing size. Family members can provide confirmation of weight loss, as can old documents such as driver's licenses. A mild, gradual weight loss occurs in some older individuals because of decreased energy requirements. However, rapid involuntary weight loss is predictive of morbidity and mortality. In addition to various disease states, causes in older individuals include loss of teeth and consequent difficulty with chewing, medications interfering with taste or causing nausea, alcohol use disorder, and social isolation. Among Black persons at an adult day health center, 65% had a significant nutritional disorder: 48.5% reported involuntary weight loss or gain, 21% ate fewer than two meals daily, and 41.2% had tooth loss or mouth pain.

Clinical Findings

Once the weight loss is established, the history, medication profile, physical examination, and conventional laboratory and radiologic investigations (eg, CBC, liver biochemical tests, kidney panel, serologic tests including HIV, TSH level, UA, fecal occult blood test, and chest radiography) usually reveal the cause. Age-appropriate cancer screening should be completed as recommended by guidelines (eg, Papanicolaou smear, mammography, fecal occult blood test/screening colonoscopy/flexible sigmoidoscopy, possibly PSA) (Chapter 1). Whole-body CT imaging is increasingly used for diagnosis; one study found its diagnostic yield to be 33.5%. When these tests are normal, the second phase of evaluation should focus on more definitive GI investigation (eg, tests for malabsorption, endoscopy). However, one prospective case study in patients with unintentional weight loss showed that colonoscopy did not find colorectal cancer if weight loss was the sole indication for the test.

If the initial evaluation is unrevealing, follow-up is preferable to further diagnostic testing. Death at 2-year follow-up was not nearly as common in patients with unexplained involuntary weight loss (8%) as in those with weight loss due to malignant (79%) and established nonmalignant diseases (19%). Psychiatric consultation should be considered when there is evidence of depression, dementia, anorexia nervosa, or other emotional problems. Ultimately, in approximately 15–25% of cases, no cause for the weight loss can be found.

Differential Diagnosis

Malignancy, GI disorders (poorly fitting dentures, cavities, swallowing or malabsorption disorders, pancreatic insufficiency), HF, HIV, tuberculosis, psychological problems (dementia, depression, paranoia), endocrine disorders (hyper-, hypothyroidism, hyperparathyroidism, hypoadrenalism), Whipple disease, eating problems (dietary restrictions, lack of money for food), social problems (alcohol use disorder, social isolation), and medication side effects are all established causes.

Treatment

Weight stabilization occurs in most surviving patients with both established and unknown causes of weight loss through treatment of the underlying disorder and caloric supplementation. Nutrient intake goals are established in relation to the severity of weight loss, in general ranging from 30 to 40 kcal/kg/day. In order of preference, route of administration options include oral, temporary nasojejunal tube, or percutaneous gastric or jejunal tube. Parenteral nutrition is reserved for patients with serious associated problems. A variety of pharmacologic agents have been proposed for the treatment of weight loss. These can be categorized into appetite stimulants (corticosteroids, progestational agents, cannabinoids, and serotonin antagonists); anabolic agents (growth hormone, ghrelin, and testosterone derivatives); and anticatabolic agents (omega-3 fatty acids, pentoxifylline, hydrazine sulfate, and thalidomide). There is no evidence that appetite stimulants decrease mortality, and they may have severe adverse side effects. The anabolic agent nandrolone decanoate reversed weight and lean tissue loss in women with HIV, and human growth hormone temporarily increased weight and

walking speed in undernourished elderly people. Yet, studies have not consistently shown mortality benefit.

Exercise training may prevent or even reverse the process of muscle wasting in HF ("cardiac cachexia"). Protein supplementation combined with resistance exercise training and aerobic activity may prevent aging-related muscle mass attenuation and functional performance. Some patients with cancer-associated weight loss may benefit from nutritional assessment and intervention as decreased food intake may be playing a role. The effectiveness, acceptability, and safety of exercise training for adults with cancer cachexia has not been established.

When to Refer

- Weight loss caused by malabsorption.
- Persistent nutritional deficiencies despite adequate supplementation.
- Weight loss as a result of anorexia or bulimia.

When to Admit

- Severe protein-energy malnutrition, including the syndromes of kwashiorkor and marasmus.
- Vitamin deficiency syndromes.
- Cachexia with anticipated progressive weight loss secondary to unmanageable psychiatric disease.
- Careful electrolyte and fluid replacement in protein-energy malnutrition and avoidance of "re-feeding syndrome."

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FATIGUE & SYSTEMIC INTOLERANCE DISEASE (Chronic Fatigue Syndrome)

ESSENTIAL INQUIRIES

- Weight loss; fever.
- Sleep-disordered breathing.
- Medications; substance use.

General Considerations

Fatigue, as an isolated symptom, accounts for 1–3% of visits to generalists. The symptom of fatigue is often poorly described and less well defined by patients than symptoms associated with specific dysfunction of organ systems. Fatigue or lassitude and the closely related complaints of weakness, tiredness, and lethargy are often attributed to overexertion, poor physical conditioning, sleep disturbance, obesity, undernutrition, and emotional problems. A history of the patient's daily living and working habits may obviate the need for extensive and unproductive diagnostic studies.

Fatigue in older adults increases the risk of developing negative health outcomes (mortality OR, 2.14), the development of disabilities in basic activities of daily living (OR 3.22), or the occurrence of physical decline (OR, 1.42).

A working case definition of chronic fatigue syndrome indicates that it is not a homogeneous abnormality, there is no single pathogenic mechanism, and no physical finding or laboratory test can be used to confirm the diagnosis. The Institute of Medicine (now called the National Academy of Medicine) has recommended using the term **systemic exertion intolerance disease.** Other conditions identified as causing chronic fatigue include myalgic encephalitis and neurasthenia, each with specific diagnostic criteria creating inconsistent diagnoses and treatment plans.

Clinical Findings

A. Fatigue

Clinically relevant fatigue is composed of three major components: generalized weakness (difficulty in initiating activities); easy fatigability (difficulty in completing activities); and mental fatigue (difficulty with concentration and memory). Important diseases that can cause fatigue include hyper- and hypothyroidism, HF, infections (endocarditis, hepatitis), COPD, interstitial lung disease, ESKD, sleep apnea, anemia, autoimmune disorders, multiple sclerosis, IBS, Parkinson disease, cerebral vascular accident, and cancer. Solution-focused therapy has a significant initial beneficial effect on the severity of fatigue and quality of life in patients with quiescent IBD.

Alcohol use disorder, vitamin C deficiency (scurvy), side effects from medications (eg, sedatives and beta-blockers), and psychological conditions (eg, insomnia, depression, anxiety, panic attacks, dysthmia, and somatic symptom disorder [formerly called somatization disorder]) may be the cause. Common outpatient infectious causes include mononucleosis and sinusitis. These conditions are usually associated with other characteristic signs, but patients may emphasize fatigue and not reveal their other symptoms unless directly asked. The lifetime prevalence of significant fatigue (present for at least 2 weeks) is about 25%. Fatigue of unknown cause or related to psychiatric illness exceeds that due to physical illness, injury, alcohol, or medications.

Although frequently associated with Lyme disease, severe fatigue as a long-term sequela is rare.

B. Systemic Intolerance Disease (Chronic Fatigue Syndrome)

Diagnosis of systemic exertion intolerance disease requires the presence of all of the following three symptoms:

1. Substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often

profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest.

2. Postexertional malaise.
3. Unrefreshing sleep.

In addition, the patient must have at least one of the following two manifestations: (1) cognitive impairment or (2) orthostatic intolerance (lightheadedness, dizziness, and headache that worsen with upright posture and improve with recumbency).

The evaluation of systemic exertion intolerance disease includes a history and physical examination as well as CBC; ESR; kidney function; serum electrolytes, glucose, creatinine, calcium; liver biochemical tests and thyroid function tests; UA; tuberculin skin test; and screening questionnaires for psychiatric disorders. Other tests to be performed as clinically indicated are serum cortisol, antinuclear antibody, rheumatoid factor, immunoglobulin levels, Lyme serology in endemic areas (although rarely a long-term complication of this infection), and HIV antibody. More extensive testing is usually unhelpful, including antibody to Epstein-Barr virus. There may be an abnormally high rate of postural hypotension.

Treatment

A. Fatigue

Resistance training and aerobic exercise lessens fatigue and improves performance for a number of chronic conditions associated with a high prevalence of fatigue, including HF, COPD, arthritis, and cancer. Continuous positive airway pressure is an effective treatment for obstructive sleep apnea. Pitolisant, a selective histamine H_3-receptor antagonist with wake-promoting effect, may reduce daytime sleepiness in patients with moderate to severe obstructive sleep apnea who refuse continuous positive airway pressure treatment.

Psychostimulants such as methylphenidate have shown inconsistent results in randomized trials of treatment of cancer-related fatigue. Modafinil and armodafinil appear to be effective, well-tolerated agents in HIV-positive patients with fatigue and as adjunctive agents in patients with depression or bipolar disorder with fatigue. Testosterone replacement in hypoandrogenic men over age 65 had no significant benefits for walking distance or vitality, as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue scale. However, men receiving testosterone reported slightly better mood and lower severity of depressive symptoms than those receiving placebo. Methylphenidate, as well as cognitive-behavioral therapy, may improve mental fatigue and cognitive function in patients with traumatic brain injury. Vitamin D treatment significantly improved fatigue in kidney transplantation patients as well as in otherwise healthy persons with vitamin D deficiency. Internet-based cognitive-behavioral therapy is effective in reducing severe fatigue in breast cancer survivors. Therapeutic Care (a complementary medicine modality that uses acupressure) reduces fatigue in some patients with breast cancer receiving chemotherapy, while moderate intensity exercise did not. Six weeks of Swedish massage therapy reduced fatigue in female breast cancer survivors who had surgery plus radiation and/or chemotherapy/chemoprevention. There is limited and preliminary evidence that rasagiline, modafinil, and doxepin are associated with improvement of fatigue in Parkinson disease. Amantadine, modafinil, and methylphenidate were not found to be superior to placebo in improving fatigue associated with multiple sclerosis and caused more frequent adverse events.

The treatment of subclinical hypothyroidism is unlikely to benefit symptoms of fatigue. Oral melatonin does not improve fatigue in patients with advanced cancer. Exceeding the RDA for protein intake does not increase muscle or physical function, nor augment anabolic response to testosterone in older men, nor reduce muscle soreness or fatigue after prolonged moderate-intensity walking exercise.

B. Systemic Intolerance Disease

A variety of agents and modalities have been tried for the treatment of systemic intolerance disease without improvement in symptoms.

Some patients with postural hypotension report response to increases in dietary sodium as well as fludrocortisone, 0.1 mg orally daily. The immunomodulator rintatolimod improved some measures of exercise performance compared with placebo in two trials (with low strength of evidence). Low-dose naltrexone is being used off-label with anecdotal reports of benefit. There is very limited evidence that dietary modification is beneficial.

Patients with systemic intolerance disease have benefited from a comprehensive multidisciplinary intervention, including optimal medical management, treating any ongoing affective or anxiety disorder pharmacologically, and implementing a comprehensive cognitive-behavioral treatment program. At present, **cognitive-behavioral therapy** and **graded exercise** are the treatments of choice for patients with systemic intolerance disease.

When to Refer

- Infections not responsive to standard treatment.
- Difficult-to-control hyper- or hypothyroidism.
- Severe psychological illness.
- Malignancy.

When to Admit

- Failure to thrive.
- Fatigue severe enough to impair activities of daily living.

Kim DY et al. Systematic review of randomized controlled trials for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). J Transl Med. 2020;18:7. [PMID: 31906979]

Knoop V et al; Gerontopole Brussels Study group. Fatigue and the prediction of negative health outcomes: a systematic review with meta-analysis. Ageing Res Rev. 2021;67:101261. [PMID: 33548508]

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ACUTE HEADACHE

ESSENTIAL INQUIRIES

- Age > 40 years.
- Rapid onset and severe intensity (ie, "thunderclap" headache), trauma, onset during exertion.
- Fever, vision changes, neck stiffness.
- HIV infection.
- Current or past history of hypertension.
- Neurologic findings (mental status changes, motor or sensory deficits, loss of consciousness).

General Considerations

Approximately 90% of people in the United States experience a headache in their lifetime. A broad range of disorders can cause headache (see Chapter 24). This section deals only with acute nontraumatic headache in adults and adolescents. The challenge in the initial evaluation of acute headache is to identify which patients are presenting with an uncommon but life-threatening condition; approximately 1% of patients seeking care in emergency department settings and considerably less in office practice settings fall into this category.

Diminution of headache in response to typical migraine therapies (such as serotonin receptor antagonists or ketorolac) does not rule out critical conditions such as subarachnoid hemorrhage or meningitis as the underlying cause. A "sentinel headache" before a subarachnoid hemorrhage is a sudden, intense, persistent headache different from previous headaches; it precedes subarachnoid hemorrhage by days or weeks and occurs in 15–60% of patients with spontaneous subarachnoid hemorrhage.

Clinical Findings

A. Symptoms

A careful history and physical examination should aim to identify causes of acute headache that require immediate treatment. These causes can be broadly classified as (1) imminent or completed vascular events (intracranial hemorrhage, thrombosis, cavernous sinus thrombosis, vasculitis, malignant hypertension, arterial dissection, cerebral venous thrombosis, transient ischemic attack, or aneurysm; (2) infections (abscess, encephalitis, or meningitis), intracranial masses causing intracranial hypertension, preeclampsia; and (3) carbon monoxide poisoning and methemoglobinemia. Having the patient carefully describe the onset of headache can help diagnose a serious cause.

Report of a sudden-onset headache that reaches maximal and severe intensity within seconds or a few minutes is the classic description of a "thunderclap" headache; it should precipitate workup for subarachnoid hemorrhage, since the estimated prevalence of subarachnoid hemorrhage in patients with thunderclap headache is 43%.

Thunderclap headache during the postpartum period precipitated by the Valsalva maneuver or recumbent positioning may indicate reversible cerebral vasoconstriction syndrome or irreversible cerebral venous sinus thrombosis. Venous-specific imaging sequences may be needed for diagnosis. Other historical features that raise the need for diagnostic testing include headache brought on by cough, exertion, or sexual activity.

The medical history can also guide the need for additional workup. Under most circumstances (including a normal neurologic examination), new headache in a patient older than 50 years or with HIV infection warrants immediate neuroimaging (Table 2–5). When the patient has a history of hypertension—particularly uncontrolled hypertension—a complete search for other features of "malignant hypertension" is appropriate to determine the urgency of control of hypertension (see Chapter 11). Headache and hypertension associated with pregnancy may be due to preeclampsia. Episodic headache associated with the triad of hypertension, palpitations, and sweats is suggestive of pheochromocytoma. In the absence of thunderclap headache, advanced age, and HIV infection, a careful physical examination and detailed neurologic examination will usually determine acuity of the workup and need for further diagnostic testing. A history consistent with

Table 2–5. Clinical features associated with acute headache that warrant urgent or emergent neuroimaging.

Indications for neuroimaging prior to lumbar puncture
Abnormal neurologic examination (particularly focal neurologic deficits)
Abnormal mental status
Abnormal funduscopic examination (papilledema; loss of venous pulsations)
Meningeal signs
Indications for emergent neuroimaging completed prior to leaving office or emergency department
Abnormal neurologic examination
Abnormal mental status
"Thunderclap" headache
HIV-positive patients with new type of headache[1]
Indications for urgent neuroimaging scheduled prior to leaving office or emergency department
Age > 50 years (normal neurologic examination) with new type of headache

[1]Use CT with or without contrast or MRI if HIV positive.
Data from American College of Emergency Physicians. Clinical policy: critical issues in the evaluation and management of patients presenting to the emergency department with acute headache. Ann Emerg Med. 2008;52:407-436.

Table 2–6. Summary likelihood ratios for individual clinical features associated with migraine diagnosis.

Clinical Feature	LR+ (95% CI)	LR– (95% CI)
Nausea	19 (15–25)	0.19 (0.18–0.20)
Photophobia	5.8 (5.1–6.6)	0.24 (0.23–0.26)
Phonophobia	5.2 (4.5–5.9)	0.38 (0.36–0.40)
Exacerbation by physical activity	3.7 (3.4–4.0)	0.24 (0.23–0.26)

hypercoagulability is associated with an increased risk of cerebral venous thrombosis.

Symptoms can also be useful for diagnosing migraine headache in the absence of the "classic" migraine pattern of scintillating scotoma followed by unilateral headache, photophobia, and nausea and vomiting (Table 2–6). The presence of three or more of these symptoms (nausea, photophobia, phonophobia, and exacerbation by physical activity) can establish the diagnosis of migraine (in the absence of other clinical features that warrant neuroimaging studies), and the presence of only one or two symptoms (provided one is not nausea) can help rule out migraine. A systematic list called the SNNOOP10 has been developed as a screening method for secondary causes of headache (Table 2–7).

B. Physical Examination

Critical components of the physical examination of the patient with acute headache include vital signs, neurologic examination, and vision testing with funduscopic examination. The finding of fever with acute headache warrants additional maneuvers to elicit evidence of meningeal inflammation, such as Kernig and Brudzinski signs. The absence of jolt accentuation of headache cannot accurately rule out meningitis. Patients older than 60 years should be examined for scalp or temporal artery tenderness.

Careful assessment of visual acuity, ocular gaze, visual fields, pupillary defects, optic disks, and retinal vein pulsations is crucial. Diminished visual acuity is suggestive of glaucoma, temporal arteritis, or optic neuritis. Ophthalmoplegia or visual field defects may be signs of venous sinus thrombosis, tumor, or aneurysm. Afferent pupillary defects can be due to intracranial masses or optic neuritis. In the setting of headache and hypertension, retinal cotton wool

Table 2–7. SNNOOP10 list of "red" flags for secondary causes of headache.

Sign or Symptom	Related Secondary Headaches
Systemic symptoms[1]	Headache attributed to infection, nonvascular intracranial disorders, carcinoid, or pheochromocytoma
Neoplasm in history	Neoplasms of the brain; metastasis
Neurologic deficit/dysfunction	Headaches attributed to vascular, nonvascular intracranial disorders; brain abscess and other infections
Onset of headache is sudden or abrupt	Subarachnoid hemorrhage and other headache attributed to cranial or cervical vascular disorders
Older age (> 50 years)	Giant cell arteritis and other headache attributed to cranial or cervical vascular disorders; neoplasms and other nonvascular intracranial disorders
Pattern change or recent onset of headache	Neoplasms, headaches attributed to vascular, nonvascular intracranial disorders
Positional headache	Intracranial hypertension or hypotension
Precipitated by sneezing, coughing, or exercise	Posterior fossa malformations; Chiari malformation
Papilledema	Neoplasms and other nonvascular intracranial disorders; intracranial hypertension
Progressive headache and atypical presentations	Neoplasms and other nonvascular intracranial disorders
Pregnancy or puerperium	Headaches attributed to cranial or cervical vascular disorders; postdural puncture headache; hypertension-related disorders (eg, preeclampsia); cerebral sinus thrombosis; hypothyroidism; anemia; diabetes mellitus
Painful eye with autonomic features	Pathology in posterior fossa, pituitary region, or cavernous sinus; Tolosa-Hunt syndrome (severe, unilateral headaches with orbital pain and ophthalmoplegia due to extraocular palsies); other ophthalmic causes
Posttraumatic onset of headache	Acute and chronic posttraumatic headache; subdural hematoma and other headache attributed to vascular disorders
Immunosuppression, eg, HIV, immunosuppressive medications	Opportunistic infections
Painkiller overuse or new drug at onset of headache	Medication overuse headache; drug incompatibility

[1]"Orange" flag for isolated fever alone.

Reproduced with permission from Do TP et al. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. Neurology. 2019;92(3):134–144. https://n.neurology.org/content/92/3/134.long.

spots, flame hemorrhages, and disk swelling indicate acute severe hypertensive retinopathy. Ipsilateral ptosis and miosis suggest Horner syndrome and in conjunction with acute headache may signify carotid artery dissection. Finally, papilledema or absent retinal venous pulsations are signs of elevated intracranial pressure—findings that should be followed by neuroimaging prior to performing lumbar puncture (Table 2–5). On nonmydriatic fundoscopy, up to 8.5% of patients who arrive at the emergency department complaining of headache had abnormalities; although few had other significant physical examination findings, 59% of them had abnormal neuroimaging studies.

Complete neurologic evaluations are also critical and should include assessment of mental status, motor and sensory systems, reflexes, gait, cerebellar function, and pronator drift. Any abnormality on neurologic evaluation (especially mental status) warrants emergent neuroimaging (Table 2–5).

C. Diagnostic Studies

Neuroimaging indications are summarized in Table 2–5. Under most circumstances, a noncontrast head CT is sufficient to exclude intracranial hypertension with impending herniation, intracranial hemorrhage, and many types of intracranial masses (notable exceptions include lymphoma and toxoplasmosis in HIV-positive patients, herpes simplex encephalitis, and brain abscess). When needed, a contrast study can be ordered to follow a normal noncontrast study. A normal neuroimaging study does not exclude subarachnoid hemorrhage and should be followed by lumbar puncture. One study supported a change of practice wherein a lumbar puncture can be withheld when a head CT scan was performed less than 6 hours after headache onset and showed no evidence of subarachnoid hemorrhage (negative predictive value 99.9% [95% CI, 99.3–100.0%]).

Based on one prospective study of 1536 emergency department patients, the yield for acute findings on head CT differed based on the indications for imaging and were 27% for seizures, 20% for confusion, 19% for syncope, 16% for focal neurologic deficit, 15% for head injury, 12% for headache, and 8% for dizziness.

In patients for whom there is a high level of suspicion for subarachnoid hemorrhage or aneurysm, a normal CT and lumbar puncture should be followed by angiography within the next few days (provided the patient is medically stable).

Lumbar puncture is also indicated to exclude infectious causes of acute headache, particularly in patients with fever or meningeal signs. Cerebrospinal fluid tests should routinely include Gram stain, WBC count with differential, RBC count, glucose, total protein, and bacterial culture. In appropriate patients, also consider testing cerebrospinal fluid for Venereal Disease Research Laboratory (syphilis), cryptococcal antigen (HIV-positive patients), acid-fast bacillus stain and culture, and complement fixation and culture for coccidioidomycosis. Storage of an extra tube with 5 mL of cerebrospinal fluid is prudent for conducting unanticipated tests in the immediate future. PCR tests for specific infectious pathogens (eg, herpes simplex 2) should also be considered in patients with evidence of CNS infection but no identifiable pathogen.

The Ottawa subarachnoid hemorrhage clinical decision rule had 100% sensitivity (and 13–15% specificity in different studies) in predicting subarachnoid hemorrhage. According to it, patients who seek medical attention in an emergency department complaining of an acute nontraumatic headache should be evaluated for subarachnoid hemorrhage if they have one or more of the following factors: age 40 years or older, neck pain or stiffness, witnessed loss of consciousness, onset during exertion, thunderclap headache (instantly peaking pain), or limited neck flexion on examination.

In addition to neuroimaging and lumbar puncture, additional diagnostic tests for exclusion of life-threatening causes of acute headache include ESR (temporal arteritis; endocarditis), UA (malignant hypertension; preeclampsia), and sinus CT (bacterial sinusitis, independently or as a cause of venous sinus thrombosis).

Treatment

Treatment should be directed at the cause of acute headache. In patients in whom migraine or migraine-like headache has been diagnosed, early treatment with ketorolac (oral, nasal, or intramuscular), dihydroergotamine, lasmiditan, ubrogepant, or triptans (oral, nasal, subcutaneous) can often abort or provide significant relief of symptoms (see Chapter 24). Intravenous prochlorperazine plus diphenhydramine was more effective for migraine pain relief than intravenous hydromorphone in the emergency department. Prochlorperazine appears to be superior to ketamine for the treatment of benign headaches (without signs or symptoms of serious intracranial pathology) in the emergency department. Sumatriptan may be less effective as immediate therapy for migraine attacks with aura compared to attacks without aura. Haloperidol (2.5 mg intravenously) given to patients in the emergency department with severe benign headache resulted in a significant reduction pain score compared with placebo. Although oral beta-blockers used for the prevention of migraine headache are not effective for the treatment of acute pain, timolol eye drops may be effective in the management of acute migraine pain.

There may be a role for oral corticosteroids to prevent rebound headache after emergency department discharge, but in one study, long-acting intramuscular methylprednisolone acetate did not decrease the frequency of post-emergency department discharge headache days compared with oral dexamethasone. Parenteral morphine and hydromorphone are best avoided as first-line therapy, although opioids are still prescribed to nearly half of all patients with acute migraine.

Subanesthetic ketamine infusions may be beneficial in individuals with chronic migraine and new daily persistent headache that has not responded to other aggressive treatments. Peripheral nerve blocks may be a safe and effective way to treat headaches in older adults. Surgical decompression of peripheral cranial and spinal nerves at trigger sites have been used to treat migraine. Noninvasive vagus nerve stimulation has shown promise in the management of migraine and acute cluster headaches.

High-flow oxygen therapy may also provide effective treatment for all headache types in the emergency

department setting (eg, benefitting older patients with cluster headaches). Peripheral nerve blocks for treatment-refractory migraine may be an effective therapeutic option in pregnancy. The oral 5-HT_{1F} receptor agonist, lasmiditan, has been approved for the acute treatment of migraine with or without aura in adults. The calcitonin gene-related peptide antagonists ("gepants") rimegepant and atogepant and the monoclonal antibodies (erenumab, fremanezumab, galcanezumab) have been approved for prevention of migraine. Ubrogepant and rimegepant have been approved for the acute treatment of migraine. Galcanezumab has activity against cluster headache. Because triptans (and ergot derivatives) are contraindicated in patients with all forms of vascular disease, the calcitonin gene-related peptide antagonists and serotonin 5-HT_{1F}-receptor agonists "ditans" (lasmiditan) may be particularly helpful in treating migraine in older patients who have increased rates of contraindications to first-line therapy. Regular exercise may have a prophylactic effect on migraine frequency; however, new, intense exercise can trigger migraine.

When to Refer

- Frequent migraines not responsive to standard therapy.
- Migraines with atypical features.
- Chronic daily headaches due to medication overuse.

When to Admit

- Need for repeated doses of parenteral pain medication.
- To facilitate an expedited workup requiring a sequence of neuroimaging and procedures.
- To monitor for progression of symptoms and to obtain neurologic consultation when the initial emergency department workup is inconclusive.
- Pain severe enough to impair activities of daily living or impede follow-up appointments or consultations.
- Patients with subarachnoid hemorrhage, intracranial mass, or meningitis.

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DYSURIA

ESSENTIAL INQUIRIES

- Fever; new back or flank pain; nausea or vomiting.
- Vaginal discharge.
- Pregnancy risk.
- Structural abnormalities.
- Instrumentation of urethra or bladder.

General Considerations

Dysuria (painful urination) is a common reason for adults and adolescents to seek urgent medical attention.

An inflammatory process (eg, bacterial UTI, herpes simplex, autoimmune disorder) underlies most causes of dysuria. In women, cystitis is diagnosed in up to 50–60% of cases. Cystitis has an incidence of 0.5–0.7% per year in sexually active young women. The key objective in evaluating women with dysuria is to exclude serious upper urinary tract disease, such as acute pyelonephritis, and sexually transmitted diseases. In elderly men, dysuria may be a symptom of prostatitis. In contrast, in younger men, urethritis accounts for most cases of dysuria. Male cyclists have no worse sexual or urinary functions than swimmers or runners, but cyclists are more prone to urethral stricture.

Clinical Findings

A. Symptoms

Well-designed cohort studies have shown that some women can be reliably diagnosed with uncomplicated cystitis without a physical examination or UA, and randomized controlled trials show that telephone management of uncomplicated cystitis is safe and effective. An increased likelihood of cystitis is present when women report multiple irritative voiding symptoms (dysuria, urgency, frequency), fever, or back pain (positive LRs = 1.6–2.0). A cohort study found that the symptom of dysuria most reliably predicted a culture-positive UTI. Inquiring about symptoms of vulvovaginitis is imperative. When women report dysuria and urinary frequency, and deny vaginal discharge and irritation, the LR for culture-confirmed cystitis is 24.5. In contrast, when vaginal discharge or

irritation is present, as well as dysuria or urinary frequency, the LR is 0.7. Gross hematuria in women with voiding symptoms usually represents hemorrhagic cystitis but can also be a sign of bladder cancer (particularly in older patients) or upper tract disease. Failure of hematuria to resolve with antibiotic treatment should prompt further evaluation of the bladder and kidneys. Chlamydial infection should be strongly considered among women aged 25 years or younger who are sexually active and seeking medical attention for a suspected UTI for the first time or who have a new partner.

Because fever and back pain as well as nausea and vomiting are clinical criteria for acute pyelonephritis, women with these symptoms should usually be examined before initiation of treatment to exclude coexistent urosepsis, hydronephrosis, or nephrolithiasis that would affect management decisions. Risk factors for acute pyelonephritis among women aged 18–49 years relate to sexual behaviors (frequent sexual intercourse [three times per week or more], new sexual partner in previous year, recent spermicide use), as well as diabetes mellitus and recent UTI or incontinence.

Finally, pregnancy, underlying structural factors (polycystic kidney disease, nephrolithiasis, neurogenic bladder), immunosuppression, diabetes mellitus, and a history of recent bladder or urethral instrumentation usually alter the treatment regimen (antibiotic choice or duration of treatment, or both) for cystitis. Presence of UTI during pregnancy is strongly associated with preeclampsia (particularly UTI during the third trimester).

B. Physical Examination

Fever, tachycardia, or hypotension suggests the possibility of urosepsis and potential need for hospitalization. A focused examination in women, in uncomplicated circumstances, could be limited to ascertainment of costovertebral angle tenderness as a finding for pyelonephritis and to a lower abdominal and pelvic examination if the history suggests vulvovaginitis or cervicitis.

C. Diagnostic Studies

1. Urinalysis—UA is probably overutilized in the evaluation of dysuria. The probability of culture-confirmed UTI among women with a history and physical examination compatible with uncomplicated cystitis is about 70–90%. UA is most helpful in atypical presentations of cystitis. Dipstick detection (greater than trace) of leukocytes, nitrites, or blood supports a diagnosis of cystitis. When both leukocyte and nitrite tests are positive, the LR is 4.2, and when both are negative, the LR is 0.3. The negative predictive value of UA is not sufficient to exclude culture-confirmed UTI in women with multiple and typical symptoms, and randomized trial evidence shows that antibiotic treatment is beneficial to women with typical symptoms and negative UA dipstick tests. Microscopy of unspun urine may also be helpful in diagnosis and reduces unnecessary use of antibiotics. The combination of urgency, dysuria, and pyuria assessed with the high-power (40×) objective for leukocytes (more than 1 leukocyte/7 high-power fields) had a positive predictive value of 71 and LR of 2.97. Urine samples produced at home rarely meet diagnostic standards.

2. Urine culture—Urine culture should be considered for all women with upper tract symptoms (prior to initiating antibiotic therapy), as well as those with dysuria and a negative urine dipstick test. In symptomatic women, a clean-catch urine culture is considered positive when 10^2–10^3 colony-forming units/mL of a uropathogenic organism are detected. The benefit of DNA next-generation sequencing and expanded quantitative urine culture is being studied, and in a recent study, multiplex polymerase chain reaction analysis was found to be as beneficial as a urine culture.

3. Renal imaging—When severe flank or back pain is present, the possibility of complicated kidney infection (perinephric abscess, nephrolithiasis) or of hydronephrosis should be considered. Renal ultrasound or CT scanning should be done to rule out abscess and hydronephrosis. To exclude nephrolithiasis, noncontrast helical CT scanning is more accurate than renal ultrasound and is the diagnostic test of choice. In a meta-analysis, the positive and negative LRs of helical CT scanning for diagnosis of nephrolithiasis were 23.2 and 0.05, respectively.

Differential Diagnosis

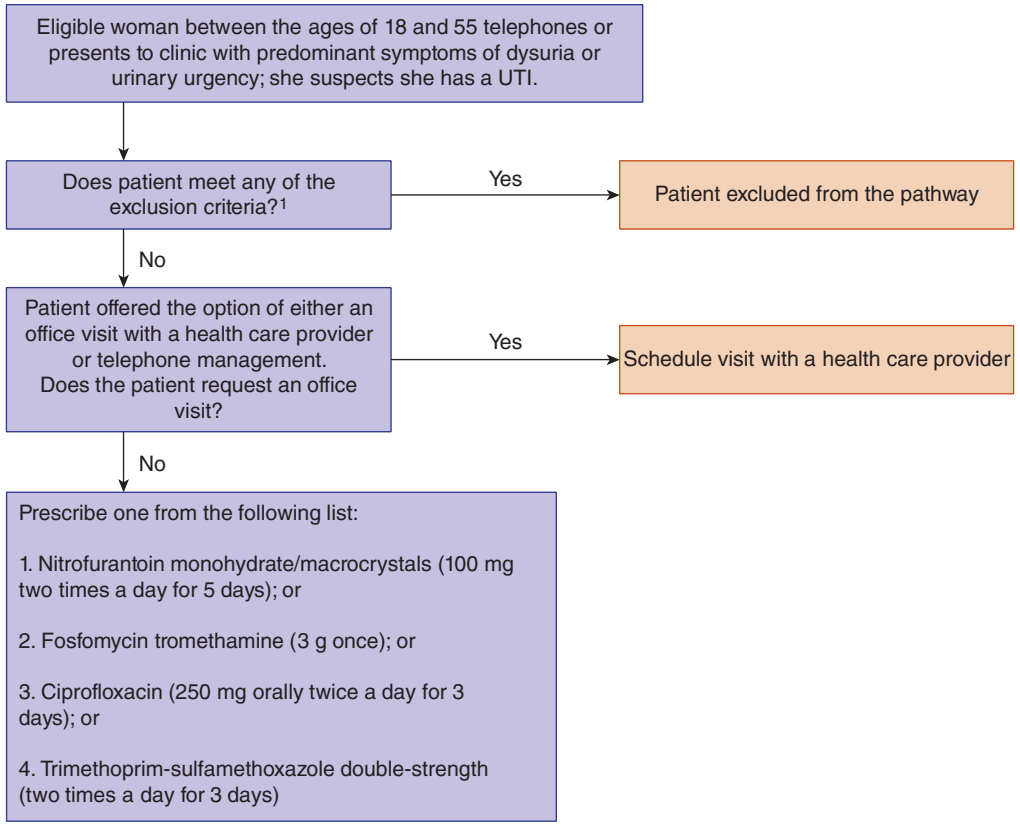
The differential diagnosis of dysuria in women includes acute cystitis, acute pyelonephritis, vaginitis (*Candida*, bacterial vaginosis, *Trichomonas*, herpes simplex), urethritis/cervicitis (*Chlamydia*, gonorrhea), and interstitial cystitis/painful bladder syndrome. Pelvic congestion syndrome (dilated and refluxing pelvic veins) may also cause dysuria and pelvic pain.

Nucleic acid amplification tests from first-void urine or vaginal swab specimens are highly sensitive for detecting chlamydial infection in men and women. Other infectious pathogens associated with dysuria and urethritis in men include *Mycoplasma genitalium* and Enterobacteriaceae.

Treatment

Definitive treatment is directed to the underlying cause of the dysuria. An evidence-informed algorithm for managing suspected UTI in women is shown in Figure 2–1. This algorithm supports antibiotic treatment of most women with multiple and typical symptoms of UTI without performing UA or urine culture. Telemedicine may be an appropriate technology to assess and manage uncomplicated UTI for average-risk patients who can self-diagnose. Antibiotic selection should be guided by local resistance patterns and expert-panel clinical practice guidelines; major options for uncomplicated cystitis include nitrofurantoin, cephalosporins, ciprofloxacin, fosfomycin, and trimethoprim-sulfamethoxazole. Five days of nitrofurantoin resulted in a significantly greater likelihood of clinical and microbiologic resolution than single-dose fosfomycin.

In a study of 47 patients with UTIs due to multidrug-resistant bacteria, treatment with fosfomycin resulted in clinical cure rates of 87% and 94% at 48 hours and 14 days, respectively.



[1]Primary exclusion criteria include documented fever 38°C; symptoms of dysuria or urgency ≥ 7 days; symptoms of vaginitis are present; abdominal pain, nausea, or vomiting; gross hematuria in patients older than 50 years; immunosuppression (eg, current use of chemotherapeutic agents); diabetes mellitus; known pregnancy; chronic renal or urologic abnormalities, other than stress urinary incontinence (eg, polycystic kidney disease, neurogenic bladder, renal failure); recent or persistent urinary stones; urinary catheterization or other urologic procedure ≤ 2 wk ago; discharge from hospital or nursing home ≤ 2 wk ago; treatment for UTI ≤ 2 wk ago; recurrent symptomatic UTI.

▲ **Figure 2–1. Proposed algorithm for evaluating women with symptoms of acute UTI.** (Data from Gupta K et al; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52:e103.)

According to the American Academy of Pediatrics' Committee on Drugs, antibiotics that are usually acceptable when treating women who are breastfeeding include trimethoprim-sulfamethoxazole (unless G6PD deficiency is present), amoxicillin, nitrofurantoin, ciprofloxacin, and ofloxacin. Plazomicin, a novel neoglycoside, is FDA approved for the treatment of adults with complicated UTIs who have limited or no alternative treatment options.

In men, prolonged treatment of UTIs (more than 7 days) out of concern for delayed clearance of infection within the prostate does not appear to reduce early or late recurrences. A 5-day course of fluoroquinolones in outpatient men with UTI is as effective as a 10-day course. Among afebrile men with symptoms of UTI, treatment with ciprofloxacin or trimethoprim/sulfamethoxazole for 7 days was noninferior to 14 days regarding resolution of UTI symptoms.

Symptomatic relief can be provided with phenazopyridine, a urinary analgesic that is available over the counter; it is used in combination with antibiotic therapy (when a UTI has been confirmed) but for no more than 2 days. Patients should be informed that phenazopyridine will cause orange/red discoloration of their urine and other body fluids (eg, some contact lens wearers have reported discoloration of their lenses). Rare cases of methemoglobinemia and hemolytic anemia have been reported, usually with overdoses or underlying kidney dysfunction. NSAIDs have also been shown to be of symptomatic benefit, but less effective than antibiotic therapy. Although some women recover from uncomplicated UTI when treated with NSAIDs alone (53% in a Norwegian study), the rate of progression to pyelonephritis was substantial. Delayed antibiotic therapy in elderly patients with UTI leads to a substantially higher rate of bloodstream infections

and all-cause mortality. If a broad-spectrum antibiotic was initially prescribed empirically for UTI and urine culture results return establishing efficacy of a narrow-spectrum antibiotic, treatment should be "de-escalated" to the narrow-spectrum antimicrobial. Among premenopausal women with recurrent UTIs, the group with increased daily water consumption had a lower mean number of cystitis episodes over a 12-month period of 1.7 compared with 3.2 in the control group and reduced number of antibiotic prescriptions (1.9 and 3.6, respectively). A systematic review and meta-analysis found D-mannose protective against recurrent UTIs. In patients with asymptomatic renal calculi and recurrent UTIs, stone extraction eliminated infections in 50% of women.

In cases of interstitial cystitis/painful bladder syndrome (see Chapter 23), patients will often respond to a multimodal approach that may include urethral/vesicular dilation, biofeedback, cognitive-behavioral therapy, antidepressants, dietary changes, vaginal emollients, and other supportive measures. Vaginal estrogen effectively relieves urinary urgency and frequency as well as recurrent UTIs related to vulvovaginal atrophy of menopause (also known as genitourinary syndrome of menopause).

A meta-analysis found that antibiotic treatment for most people with asymptomatic bacteriuria is not beneficial and may be harmful. Antibiotic treatment does benefit both pregnant women with asymptomatic bacteriuria as well as persons about to undergo urologic surgery. The USPSTF recommends screening pregnant women for asymptomatic bacteriuria by obtaining a urine culture (B recommendation). The USPSTF recommends against screening for asymptomatic bacteriuria in nonpregnant adults (D recommendation).

There were no differences in the prevalence of postoperative UTI in women who had mixed-flora on preoperative urine cultures compared to those with no growth on preoperative urine cultures.

When to Refer

- Anatomic abnormalities leading to repeated urinary infections.
- Infections associated with nephrolithiasis.
- Persistent interstitial cystitis/painful bladder syndrome.

When to Admit

- Severe pain requiring parenteral medication or impairing ambulation or urination (such as severe primary herpes simplex genitalis).
- Dysuria associated with urinary retention or obstruction.
- Pyelonephritis with ureteral obstruction.
- Symptoms and signs suggesting urosepsis.

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3 Preoperative Evaluation & Perioperative Management

Hugo Q. Cheng, MD

EVALUATION OF THE ASYMPTOMATIC PATIENT

Patients without significant medical problems—especially those under age 50—are at very low risk for perioperative complications. Their preoperative evaluation should include a history and physical examination; emphasis should be on a pharmacologic history and assessment of functional status, exercise tolerance, and cardiopulmonary status to look for unrecognized disease that may require further evaluation prior to surgery. In addition, a directed bleeding history (Table 3–1) should be taken to uncover coagulopathy that could contribute to excessive surgical blood loss. Routine preoperative laboratory tests in asymptomatic healthy patients under age 50 have *not* been found to help predict or prevent complications. Even elderly patients undergoing minor or minimally invasive procedures (such as cataract surgery) are unlikely to benefit from preoperative screening tests.

Siddaiah H et al. Preoperative laboratory testing: implications of "Choosing Wisely" guidelines. Best Pract Res Clin Anaesthesiol. 2020;34:303. [PMID: 32711836]

CARDIAC RISK ASSESSMENT & REDUCTION IN NONCARDIAC SURGERY

The most important perioperative cardiac complications are MI and cardiac death. Other complications include heart failure (HF), arrhythmias, and unstable angina. The principal patient-specific risk factor for cardiac complications is the presence of end-organ CVD. This includes not only CAD and HF but also CVD and CKD. Diabetes mellitus, especially if treated with insulin, is considered a CVD equivalent that increases the risk of cardiac complications. Major abdominal, thoracic, and vascular surgical procedures (especially AAA repair) carry a higher risk of postoperative cardiac complications. These risk factors were identified in a validated, multifactorial risk prediction tool: the Revised Cardiac Risk Index (RCRI) (Table 3–2). The American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) risk prediction tool uses patient age, the location or type of operation, serum creatinine greater than 1.5 mg/dL (132.6 mcmol/L), dependency in activities of daily living, and the patient's American Society of Anesthesiologists physical status classification as predictors for postoperative MI or cardiac arrest. An online risk calculator using the NSQIP tool can be found at https://qxmd.com/calculate/calculator_245/gupta-perioperative-cardiac-risk. The American College of Cardiology and American Heart Association endorse both prediction tools. Patients with two or more RCRI predictors or a risk of perioperative MI or cardiac arrest in excess of 1% as calculated by the NSQIP prediction tool are deemed to be at elevated risk for cardiac complications.

Limited exercise capacity (eg, the inability to walk for two blocks at a normal pace or climb a flight of stairs without resting) also predicts higher cardiac risk. Emergency operations are also associated with greater cardiac risk but should not be delayed for extensive cardiac evaluation. Instead, patients facing emergency surgery should be medically optimized for surgery as quickly as possible and closely monitored for cardiac complications during the perioperative period.

Table 3–1. Directed bleeding history: Findings suggestive of a bleeding disorder.

Unprovoked bruising on the trunk of > 5 cm in diameter
Frequent unprovoked epistaxis or gingival bleeding
Menorrhagia with iron deficiency
Hemarthrosis with mild trauma
Prior excessive surgical blood loss or reoperation for bleeding
Family history of abnormal bleeding
Presence of severe kidney or liver disease
Use of medications that impair coagulation, including nutritional supplements and herbal remedies

Role of Preoperative Noninvasive Ischemia Testing

Most patients can be accurately risk-stratified by history and physical examination. A resting ECG should be obtained in patients with at least one RCRI predictor prior to major surgery but generally omitted in asymptomatic patients undergoing minor operations. Additional noninvasive ischemia

Table 3–2. Revised Cardiac Risk Index (RCRI).

Independent Predictors of Postoperative Cardiac Complications	
Intrathoracic, intraperitoneal, or suprainguinal vascular surgery	
History of ischemic heart disease	
History of heart failure	
Insulin treatment for diabetes mellitus	
Serum creatinine level > 2 mg/dL (> 176.8 mcmol/L)	
History of cerebrovascular disease	
Scoring (Number of Predictors Present)	**Risk of Major Cardiac Complications[1]**
None	0.4%
One	1%
Two	2.4%
More than two	5.4%

[1]Cardiac death, MI, or nonfatal cardiac arrest.
Data from Devereaux PJ et al. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ. 2005;173:627.

testing rarely improves risk stratification or management, especially in patients without CVD undergoing minor operations, or who have at least fair functional capacity. Stress testing has more utility in patients with elevated risk scores on clinical prediction tools, especially if they have poor functional status. In these patients, the absence of ischemia on dipyridamole scintigraphy or dobutamine stress echocardiography is reassuring; in contrast, extensive inducible ischemia predicts a high risk of cardiac complications, particularly with vascular surgery, which may not be modifiable by either medical management or coronary revascularization. The predictive value of an abnormal stress test result for nonvascular surgery patients is less well established. An approach to perioperative cardiac risk assessment and management in patients with known or suspected stable CAD is shown in Figure 3–1.

Role of Cardiac Biomarkers

Preoperative BNP or N-terminal fragment of proBNP (NT-proBNP) levels directly correlate with the risk for perioperative cardiac complications, and their measurement may improve risk assessment. A meta-analysis of 2179 patients found that BNP of 92 mg/L or higher or NT-proBNP of 300 ng/L or higher before noncardiac surgery were associated with a fourfold increase in 30-day mortality and MI. American and European cardiology society guidelines are equivocal about the use of biomarkers to enhance risk prediction; the Canadian Cardiovascular Society, however, strongly recommends measuring BNP or NT-proBNP levels prior to major noncardiac surgery in patients older than 65 years and younger patients with CVD or a RCRI score greater than or equal to 1.

Perioperative Management of Patients with Coronary Artery Disease

Patients with acute coronary syndromes require immediate management of their cardiac disease prior to any preoperative evaluation (see Chapter 10).

A. Medications

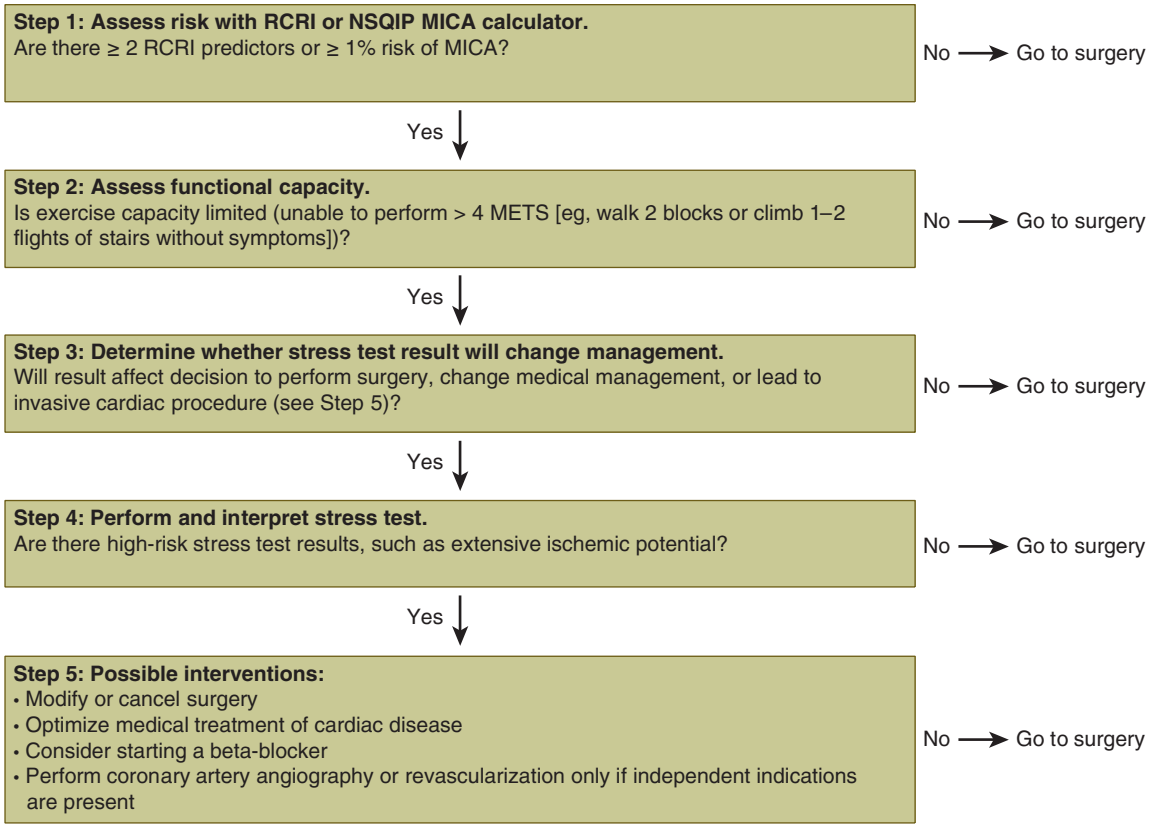
1. Antianginal medications—Preoperative antianginal medications, including beta-blockers, calcium channel blockers, and nitrates, should be continued throughout the perioperative period. Several trials have shown that initiation of beta-blockers before major noncardiac surgery reduces the risk of nonfatal MI. However, in the largest trial, a high, fixed dose of metoprolol succinate *increased* total mortality and the risk of stroke. Because of the uncertain benefit-to-risk ratio, initiation of perioperative beta-blockade should be considered only in patients with a high risk of cardiac complications. If used, beta-blockers should be started well in advance of surgery, to allow time to gradually titrate up the dose without causing excessive bradycardia or hypotension. They should not be started on the day of surgery. Possible indications and starting doses for prophylactic beta-blockade are presented in Table 3–3.

2. Statins—Several randomized trials found that HMG-CoA reductase inhibitors (statins) prevent MI in patients undergoing noncardiac surgery. Safety concerns, such as liver failure or rhabdomyolysis, have not materialized in these studies. It is unclear how far in advance of surgery statins must be started and what doses are needed to see benefits. However, based on treatment protocols used in clinical trials, at least a moderate statin dose (eg, atorvastatin 20 mg or fluvastatin 80 mg orally daily) should be considered in all patients undergoing vascular surgery and other patients deemed to be at high risk for cardiac complications, regardless of lipid levels, and initiated at least 30 days before surgery if possible. Patients already taking statins should continue these agents during the perioperative period.

3. Aspirin—In patients without coronary stents, initiation of aspirin therapy before noncardiac surgery is not recommended because it did not reduce cardiac risk and caused increased bleeding in a large, randomized trial. Holding long-term prophylactic aspirin therapy in such patients does not increase cardiac risk.

B. Coronary Revascularization

A trial that randomized over 500 patients with angiographically proven CAD to either coronary revascularization (with either coronary artery bypass grafting [CABG] or percutaneous coronary interventions [PCI]) or medical management alone before vascular surgery found no difference in postoperative MI, 30-day mortality, and long-term mortality. Thus, **preoperative CABG or PCI should be performed only when patients have guideline-concordant indications independent of the planned noncardiac operation.** In addition, surgical patients who have undergone recent coronary stenting are at high risk for stent thrombosis, especially if antiplatelet therapy is stopped prematurely. **Therefore, elective surgery should be**



Notes:

Step 2: Reasonable to avoid stress test in patients with excellent functional capacity (> 10 METs) and not unreasonable to avoid stress test in patients with moderate or good functional capacity (4–10 METs); patients with unknown functional capacity should be considered unable to perform 4 METs.

Step 3: Regardless of decision to perform stress test, patients should receive optimal guideline-concordant medical therapy.

Step 4: Pharmacologic stress test preferred due to assumption of poor exercise capacity.

Step 5: Possible indications for beta-blockers include ≥ 3 RCRI predictors, ischemia on stress test, or indications independent of surgery.

▲ **Figure 3–1.** Approach to cardiac evaluation in stable patients undergoing major elective surgery. METs, metabolic equivalents; NSQIP MICA, National Surgical Quality Improvement Program Myocardial Infarction and Cardiac Arrest; RCRI, Revised Cardiac Risk Index.

Table 3–3. Indications for prophylactic perioperative beta-blockade.[1]

Strong indications	Patient already taking beta-blocker to treat ischemia, arrhythmia, or hypertension
Possible indications	Patient with myocardial ischemia detected on preoperative stress testing Patient has ≥ 3 Revised Cardiac Risk Index predictors (see Table 3–2)

[1]Initial dose recommendations: atenolol 25 mg orally daily, bisoprolol 2.5 mg orally daily, or metoprolol tartrate 25 mg orally twice daily. The dose of beta-blocker should be carefully titrated to keep heart rate < 70 beats per minute and systolic blood pressure > 100 mm Hg. Avoid initiating beta-blockade on the day of surgery.

deferred for at least 30 days after placement of a bare-metal stent and ideally for 6 months after placement of a drug-eluting stent. If this delay poses significant risks, such as in patients undergoing an operation for cancer, surgery could be considered 3 months after drug-eluting stent implantation. Antiplatelet agents should be continued perioperatively if possible or resumed as soon as possible after surgery. The patient, surgeon, anesthesiologist, and cardiologist should discuss risks and benefits of delaying surgery and management options for dual antiplatelet therapy.

Heart Failure & LV Dysfunction

Elective surgery should be postponed until decompensated HF (manifested by an elevated jugular venous

pressure, an audible third heart sound, or evidence of pulmonary edema) has been brought under control. In patients with compensated HF, the risk of perioperative cardiac complications is similar in patients with ischemic or nonischemic cardiomyopathy. HF with reduced EF likely confers more risk than HF with preserved EF. Guidelines recommend preoperative echocardiography to evaluate LV function in patients without known HF who have unexplained dyspnea and in patients with known HF with clinical deterioration.

Patients receiving diuretics and digoxin should have serum electrolyte and digoxin levels measured prior to surgery because abnormalities in these levels may increase the risk of perioperative arrhythmias. Clinicians must be cautious not to give too much diuretic, since the volume-depleted patient will be much more susceptible to intraoperative hypotension. The surgeon and anesthesiologist should be made aware of the presence and severity of LV dysfunction so that appropriate decisions can be made regarding perioperative fluid management and intraoperative monitoring.

Postoperative MI

In a large cohort study, postoperative MI (defined by a combination of ECG abnormality and cardiac enzyme elevation) typically occurred within 3 days of surgery and was asymptomatic in the majority of cases. Clinical findings that should prompt its consideration include unexplained hypotension, hypoxemia, and delirium. Postoperative MI is associated with increased mortality, even when asymptomatic. Elevated postoperative troponin levels correlate directly with mortality risk, even in patients without ECG abnormalities or other findings of myocardial ischemia. The Canadian Cardiovascular Society advocates routine postoperative screening of high-risk patients with troponin levels, while American and European guidelines remain equivocal. It remains unclear how asymptomatic postoperative MI or troponin elevation should be managed, but optimizing secondary cardiac risk reduction strategies is reasonable.

Valvular Heart Disease

If the nature or severity of valvular lesions is unknown, or if there has been a recent change in clinical status, echocardiography should be performed prior to noncardiac surgery. In addition, patients with known or suspected stenotic or regurgitant valvular disease that is moderately severe or worse should undergo echocardiography within 1 year before surgery. Candidates for valvular intervention independent of the planned noncardiac surgery should have the valve correction procedure performed first. Patients with uncorrected critical or symptomatic aortic stenosis are at particular risk for cardiac complications. They should undergo surgery only after consultation with a cardiologist and anesthesiologist. Patients with mitral stenosis require heart rate control to prolong diastolic filling time. Regurgitant valvular lesions are generally less problematic during surgery because the vasodilatory effect of anesthetics promotes forward flow. Patients with aortic or mitral regurgitation likely benefit from afterload reduction and careful attention to volume status, but negative chronotropes may worsen the regurgitant volume and should be avoided.

Arrhythmias

The finding of a rhythm disturbance on preoperative evaluation should prompt consideration of further cardiac evaluation, particularly when the finding of structural heart disease would alter perioperative management. **Patients with a rhythm disturbance without evidence of underlying heart disease are at low risk for perioperative cardiac complications.** While long-term antiarrhythmic medications should be continued perioperatively, there is no evidence that the use of medications to suppress an asymptomatic arrhythmia alters perioperative risk.

Patients with symptomatic arrhythmias should not undergo elective surgery until their cardiac condition has been addressed. Adequate rate control of atrial fibrillation or other supraventricular arrhythmias should be established prior to surgery. Symptomatic ventricular tachycardia must be thoroughly evaluated and controlled prior to surgery. Patients who have independent indications for a permanent pacemaker or implanted defibrillator should have it placed prior to noncardiac surgery. The anesthesiologist must be notified that a patient has an implanted pacemaker or defibrillator to prevent device malfunction from intraoperative electrocautery.

After major surgery, previously undiagnosed atrial fibrillation develops in approximately 1% of patients. Most episodes resolve spontaneously within hours to days. These patients, however, have an increased risk for subsequent atrial fibrillation and an elevated risk of stroke. Whether the same criteria for anticoagulation therapy should be used for patients undergoing surgery as for patients not undergoing surgery is unclear.

Hypertension

No evidence supports delaying surgery in order to better control mild to moderate hypertension (systolic blood pressure below 180 mm Hg and diastolic blood pressure below 110 mm Hg). Severe hypertension (systolic pressure greater than 180 mm Hg or a diastolic pressure greater than 110 mm Hg) appears to be an independent predictor of perioperative cardiac complications, including MI and HF. It is reasonable to consider delaying elective surgery in patients with such severe hypertension until blood pressure can be controlled, although it is not known whether the risk of cardiac complications is reduced with this approach.

Most medications for chronic hypertension should generally be continued up to and including the day of surgery. Cardiology societies' guidelines differ in their recommendation on whether to continue or hold ACE inhibitors and ARBs on the day of surgery. Continuation increases the risk of intraoperative and postoperative hypotension, whereas holding these agents increases postoperative hypertension. Diuretic agents are frequently held on the

day of surgery to prevent hypovolemia and electrolyte disorders if they are not needed to control HF; however, the benefit of this practice is uncertain.

Patients without chronic hypertension may manifest hypertension after surgery, and patients being treated for hypertension often experience decreased control of their blood pressure. Potential causes include elevated sympathetic tone due to injury or pain, volume overload from intravenous fluids, hypercarbia, urine retention, and withholding long-term antihypertensive medications. Before initiating postoperative medical management of hypertension, reversible contributors should be addressed.

Fleisher LA et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64:e77. [PMID: 25091544]

Hanley C et al. Perioperative risk assessment—focus on functional capacity. Curr Opin Anaesthesiol. 2021;34:309. [PMID: 33935179]

Smilowitz NR et al. Perioperative cardiovascular risk assessment and management for noncardiac surgery: a review. JAMA. 2020;324:279. [PMID: 32692391]

PULMONARY EVALUATION IN NON–LUNG RESECTION SURGERY

Pneumonia and respiratory failure requiring prolonged mechanical ventilation are the most important postoperative pulmonary complications. The occurrence of these complications has been associated with a significant increase in mortality and hospital length of stay. Pulmonary thromboembolism is another serious complication; prophylaxis against venous thromboembolic disease is detailed in Table 14–14.

Risk Factors for the Development of Postoperative Pulmonary Complications

Procedure-related risk factors for postoperative pulmonary complications include location of surgery (highest rates occur in cardiac, thoracic, and upper abdominal cases), prolonged anesthesia, and emergency cases. Operations not requiring general anesthesia tend to have lower rates of postoperative pulmonary complications; laparoscopic procedures tend to have lower risk than comparable open procedures.

A summary of patient-specific risk factors for pulmonary complications is presented in Table 3–4. Advanced age appears to confer increased risk. The presence and severity of systemic disease of any type is associated with pulmonary complications. In particular, patients with COPD or HF have at least twice the risk of postoperative pulmonary complications compared with patients without these conditions. As with preoperative cardiac risk assessment, physical debility and poor functional capacity predict higher risk of postoperative pulmonary complications. A risk calculator for predicting postoperative respiratory failure based on the NSQIP patient database is available (https://qxmd.com/calculate/calculator_261/postoperative-respiratory-failure-risk-calculator).

Table 3–4. Clinical risk factors for postoperative pulmonary complications.

Upper abdominal or cardiothoracic surgery
Prolonged anesthesia time (> 4 hours)
Emergency surgery
Age > 60 years
COPD
Heart failure
Severe systemic disease
Tobacco use (> 20 pack-years)
Impaired cognition or sensorium
Functional dependency or prior stroke
Preoperative sepsis
Low serum albumin level
Obstructive sleep apnea

Pulmonary Function Testing & Laboratory Studies

The main role for preoperative pulmonary function testing (PFT) is to identify pulmonary disease in patients with unexplained symptoms prior to major abdominal or cardiothoracic surgery. In patients with diagnosed lung disease, PFT often add little information above clinical assessment. Chest radiographs in unselected patients also rarely add clinically useful information. The benefit of polysomnography to diagnose obstructive sleep apnea prior to bariatric surgery is unproven. Arterial blood gas measurement is not routinely recommended except in patients with known lung disease and suspected hypoxemia or hypercapnia.

Preoperative Risk Reduction

Retrospective studies have shown that smoking cessation reduced the incidence of pulmonary complications, but only if it was initiated at least 1–2 months before surgery. A meta-analysis of randomized trials found that preoperative smoking cessation programs reduced both pulmonary and surgical wound complications, especially if smoking cessation was initiated at least 4 weeks prior to surgery. **The preoperative period may be an optimal time to initiate smoking cessation efforts.** A systematic review found that smoking cessation programs started in a preoperative evaluation clinic increased the odds of abstinence at 3–6 months by nearly 60%. Patients who have recovered from SARS-CoV-2 infection appear to have elevated surgical mortality up to 7 weeks after diagnosis. Increased mortality was observed even after mild or asymptomatic cases, and the risk persisted beyond 7 weeks in patients who were still symptomatic at that time. Elective surgery should not be scheduled within 7 weeks of SARS-CoV-2 infection for patients whose symptoms have resolved or longer while patients remain symptomatic.

Postoperative Risk Reduction

Postoperative risk reduction strategies have centered on promoting lung expansion through the use of incentive

spirometry; deep breathing exercises; and in selected populations, continuous positive airway pressure (CPAP) or intermittent positive-pressure breathing (IPPB). Although trial results have been mixed, all these techniques have been shown to reduce the incidence of postoperative atelectasis and, in a few studies, to reduce the incidence of other postoperative pulmonary complications. In most comparative trials, these methods were equally effective. Given the higher cost of CPAP and IPPB, **incentive spirometry and deep breathing exercises are the preferred methods for most patients.** Multi-component respiratory care programs may be particularly beneficial. One program termed "I COUGH"—an acronym for *I*ncentive spirometry, *C*oughing and deep breathing, *O*ral care, *U*nderstanding (patient education), *G*et out of bed (early ambulation), and *H*ead of bed elevation—reduced the rates of pneumonia and unplanned intubation after general and vascular surgery.

Lumb AB. Pre-operative respiratory optimisation: an expert review. Anaesthesia. 2019;74:43. [PMID: 30604419]
Selzer A et al. Preoperative pulmonary evaluation. Med Clin North Am. 2019;103:585. [PMID: 30955524]

EVALUATION OF THE PATIENT WITH LIVER DISEASE

Patients with serious liver disease are at increased risk for perioperative morbidity, and decompensated liver disease is associated with an extremely high perioperative mortality. Appropriate preoperative evaluation requires consideration of the effects of anesthesia and surgery on postoperative liver function and of the complications associated with anesthesia and surgery in patients with preexisting liver disease.

Risk Assessment in Surgical Patients with Liver Disease

Screening unselected patients with liver biochemical tests has a low yield and is not recommended. Patients with suspected or known liver disease based on history or physical examination, however, should have measurement of liver enzyme levels as well as tests of hepatic synthetic function performed prior to surgery.

Elective surgery in patients with acute viral or alcoholic hepatitis should be delayed until the acute episode has resolved. In three small series of patients with acute viral hepatitis who underwent abdominal surgery, the mortality rate was roughly 10%. Similarly, patients with undiagnosed alcoholic hepatitis had high mortality rates when undergoing abdominal surgery. In the absence of cirrhosis or synthetic dysfunction, chronic viral hepatitis is unlikely to increase risk significantly. Similarly, nonalcoholic fatty liver disease without cirrhosis probably does not pose a serious risk in surgical patients.

In patients with cirrhosis, postoperative complication rates correlate with the severity of liver dysfunction. Traditionally, severity of dysfunction has been assessed with the Child-Pugh score (see Chapter 16). A conservative approach would be to avoid elective surgery in patients with Child-Pugh class C cirrhosis and pursue it with great caution in class B patients. The Model for End-stage Liver Disease (MELD) score, based on serum bilirubin and creatinine levels, and the prothrombin time expressed as the INR, also predicted surgical mortality and outperformed the Child-Pugh classification in some studies. A web-based risk assessment calculator incorporating age and MELD score can predict both perioperative and long-term mortality (https://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/post-operative-mortality-risk-patients-cirrhosis). Generally, a MELD score less than 10 predicts low risk, whereas a score greater than 16 portends high mortality after elective surgery.

When surgery is elective, controlling ascites, encephalopathy, and coagulopathy preoperatively is prudent. Ascites is a particular problem in abdominal operations, where it can lead to wound dehiscence and hernias. Great care should be taken when using analgesics and sedatives, since these can worsen hepatic encephalopathy; in general, short-acting agents and lower doses should be used. Postoperative constipation should be aggressively treated because it can precipitate encephalopathy. Kidney function and volume status need to be closely monitored to prevent AKI and volume overload, which are common complications in these patients. Patients with coagulopathy should receive vitamin K and may need fresh frozen plasma transfusion at the time of surgery; however, transfusing to a specific INR target for cirrhosis is discouraged.

Northup PG et al. AGA Clinical Practice Update: surgical risk assessment and perioperative management in cirrhosis. Clin Gastroenterol Hepatol. 2019;17:595. [PMID: 30273751]

PREOPERATIVE HEMATOLOGIC EVALUATION

Three of the more common clinical situations faced by the medical consultant are the patient with anemia, the assessment of bleeding risk, and the perioperative management of long-term anticoagulation.

The main goals of the preoperative evaluation of the anemic patient are to determine the need for preoperative diagnostic evaluation and the need for transfusion. **When feasible, the diagnostic evaluation of the patient with previously unrecognized anemia should be done prior to surgery because certain types of anemia (particularly those due to sickle cell disease, hemolysis, and acute blood loss) have implications for perioperative management.** These types of anemia are typically associated with an elevated reticulocyte count. Given the prevalence of iron deficiency, excluding it as the cause of anemia is reasonable. However, the practice of administering intravenous iron to unselected anemic patients before elective surgery has not been proven beneficial. Preoperative anemia is associated with higher perioperative morbidity and mortality. Whether raising preoperative hemoglobin level to specific targets will improve postoperative outcomes is unknown. The clinician determining the need for preoperative transfusion in an individual patient must consider factors other than the absolute hemoglobin level, including

Table 3–5. Recommendations for perioperative management of DOACs.

Drug and Kidney Function	Last Dose Before Procedure	Resume Medication
Dabigatran with normal creatinine clearance (> 50 mL/min [0.83 mL/s]); rivaroxaban, apixaban, edoxaban	2 days before procedure with low risk of bleeding or 3 days before procedure with high risk of bleeding	If hemostasis adequate, resume 24 hours after procedure with low risk of bleeding or 48–72 hours after procedure with high risk of bleeding
Dabigatran with reduced creatinine clearance (30–50 mL/min [0.5–0.83 mL/s)	3 days before procedure with low risk of bleeding or 5 days before procedure with high risk of bleeding	

the presence of cardiopulmonary disease, the type of surgery, and the likely severity of surgical blood loss. The few studies that have compared different postoperative transfusion thresholds failed to demonstrate improved outcomes with a more aggressive transfusion strategy. Based on available evidence, the AABB (formerly American Association of Blood Banks) recommends transfusion for a hemoglobin level less than 8 g/dL (80 g/L) or for symptomatic anemia in patients undergoing orthopedic or cardiac surgery.

The most important component of the bleeding risk assessment is a directed bleeding history (see Table 3–1). Patients who provide a reliable history of no abnormal bleeding on directed bleeding history and have no suggestion of abnormal bleeding on physical examination are at very low risk for having an occult bleeding disorder. Laboratory tests of hemostatic parameters in these patients are generally not needed. When the directed bleeding history is unreliable or incomplete, or when abnormal bleeding is suggested, a formal evaluation of hemostasis should be done prior to surgery and should include measurement of the prothrombin time, activated partial thromboplastin time, and platelet count (see Chapter 13).

Patients receiving long-term oral anticoagulation are at risk for thromboembolic complications when an operation requires interruption of this therapy. However, "bridging anticoagulation," where unfractionated or low-molecular-weight heparin is administered parenterally while oral anticoagulants are held, has not been shown to be beneficial and can increase bleeding. A cohort study found that DOACs could be safely managed without bridging by using a protocol based on the patient's kidney function where the DOACs are withheld several days prior to surgery and restarted 24–48 hours after surgery if hemostasis appears adequate (Table 3–5). A randomized trial of bridging anticoagulation in surgical patients taking warfarin for atrial fibrillation demonstrated no difference in thromboembolism. Bleeding complications were twice as common in patients who received bridging anticoagulation. A trial of postoperative bridging anticoagulation that included patients with atrial fibrillation or mechanical prosthetic heart valves also found no benefit for stroke prevention. **Most experts recommend bridging therapy only in patients at high risk for thromboembolism.** An approach to perioperative anticoagulation management with warfarin is shown in Table 3–6, but the recommendations must

Table 3–6. Recommendations for management of perioperative anticoagulation with warfarin.

Thromboembolic Risk without Anticoagulation	Recommendation
Low (eg, atrial fibrillation with $CHADS_2$ score 0–4,[1] mechanical bileaflet aortic valve prosthesis, or single venous thromboembolism > 3 months ago without hypercoagulability condition[2])	Stop warfarin 5 days before surgery Measure INR the day before surgery to confirm that it is acceptable (< 1.6 for most operations) Resume warfarin when hemostasis permits No bridging with parenteral anticoagulants before or after surgery
High (eg, either atrial fibrillation or mechanical heart valve with stroke < 3 months prior, atrial fibrillation with $CHADS_2$ score 5 or 6, mechanical mitral valve prosthesis, caged-ball or tilting disk valve prosthesis, or venous thrombosis < 3 months ago or associated with hypercoagulability condition[2])	Stop warfarin 5 days before surgery Begin bridging with therapeutic dose UFH infusion or LMWH 2 days after stopping oral anticoagulation Administer last dose of LMWH 24 hours before surgery; discontinue UFH 4–6 hours before surgery Measure INR the day before surgery to confirm that it is acceptable (< 1.6 for most operations) Resume warfarin when hemostasis permits If hemostasis permits, consider bridging with therapeutic dose UFH infusion or LMWH beginning 48–72 hours after surgery and continuing until the INR is therapeutic

[1]1 point each for heart failure, hypertension, diabetes mellitus, and age > 75 years, and 2 points for stroke or transient ischemic attack.
[2]Patients should receive venous thromboembolism prophylaxis after surgery (see Chapter 14).
LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

be considered in the context of patient preference and hemorrhagic risk.

Douketis JD et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. JAMA Intern Med. 2019;179:1469. [PMID: 31380891]
Kuo HC et al. Thromboembolic and bleeding risk of periprocedural bridging anticoagulation: a systematic review and meta-analysis. Clin Cardiol. 2020;43:441. [PMID: 31944351]
Shander A et al. How I treat anemia in the perisurgical setting. Blood. 2020;136:814. [PMID: 32556314]

NEUROLOGIC EVALUATION

Delirium can occur after any major operation but is particularly common after hip fracture repair and cardiovascular surgery, where the incidence is 30–60%. **Postoperative delirium has been associated with higher rates of major postoperative cardiac and pulmonary complications, poor functional recovery, increased length of hospital stay, increased risk of subsequent dementia and functional decline, and increased mortality.** The American Geriatrics Society recommends screening preoperative patients for these delirium risk factors: age greater than 65 years, chronic cognitive impairment or dementia, severe illness, poor vision or hearing, and the presence of infection. Patients with any of these risk factors should be enrolled in a multicomponent, nonpharmacologic delirium prevention program after surgery, which includes interventions such as reorientation, sleep hygiene, bowel and bladder care, mobilization and physical therapy, and the elimination of unnecessary medications. Moderate-quality evidence supports the use of these nonpharmacologic interventions.

Only a minority of patients with postoperative delirium will have a single, reversible etiology for their condition (see Delirium, Chapter 4). Evaluation of delirious patients should exclude electrolyte derangements, occult UTI, and adverse effects from psychotropic medications such as opioids, sedatives, anticholinergic agents, and antispasmodics. Conservative management includes reassuring and reorienting the patient; eliminating unneeded medications, intravenous lines, and urinary catheters; and keeping the patient active during the day while allowing uninterrupted sleep at night. Use of multimodal postoperative analgesic strategies can reduce or avoid the need for opioids. When agitation jeopardizes patient or provider safety, neuroleptic agents given at the lowest effective dose for the shortest duration needed are preferred over the use of benzodiazepines or physical restraints (Table 25–1).

Stroke complicates less than 1% of all surgical procedures but may occur in 1–6% of patients undergoing cardiac or carotid artery surgery. Most of the strokes in cardiac surgery patients are embolic in origin, and about half occur within the first postoperative day. A retrospective analysis found that patients who had previously suffered a stroke had an 18% risk of MI, recurrent stroke, or cardiac death if they underwent noncardiac surgery within 3 months of the stroke. This risk declined over time and reached its nadir 9 months after the stroke, suggesting a benefit to delaying elective surgery.

Symptomatic carotid artery stenosis is associated with a high risk of stroke in patients undergoing cardiac surgery. In general, patients with independent indications for correction of carotid stenosis should have the procedure done prior to elective surgery. In contrast, most studies suggest that asymptomatic carotid bruits and asymptomatic carotid stenosis are associated with little or no increased risk of stroke in surgical patients.

Benesch C et al. Perioperative neurological evaluation and management to lower the risk of acute stroke in patients undergoing noncardiac, nonneurological surgery: a scientific statement from the American Heart Association/American Stroke Association. Circulation. 2021;143:e923. [PMID: 33827230]
Jin Z et al. Postoperative delirium: perioperative assessment, risk reduction, and management. Br J Anaesth. 2020;125:492. [PMID: 32798069]

MANAGEMENT OF ENDOCRINE DISEASES

Diabetes Mellitus

The goal of management for all diabetic patients is the prevention of severe hyper- or hypoglycemia in the perioperative period. In addition, patients with type 1 diabetes are at risk for developing ketoacidosis. Increased secretion of cortisol, epinephrine, glucagon, and growth hormone during and after surgery causes insulin resistance and hyperglycemia in diabetic patients. Conversely, reduced caloric intake after surgery and frequent, unpredictable periods of fasting increase the risk for hypoglycemia. Thus, all surgical diabetic patients require frequent blood glucose monitoring. Ideally, patients with diabetes should undergo surgery early in the morning. The specific pharmacologic management of diabetes during the perioperative period depends on the type of diabetes (insulin-dependent or not), the level of glycemic control, and the type and length of surgery.

Poor preoperative glycemic control, as indicated by an elevated hemoglobin A_{1c} level, is associated with a greater risk of surgical complications, particularly infections. However, a strategy of delaying surgery until glycemic control improves has not been rigorously studied. The ideal postoperative blood glucose target is also unknown. Based on trials that showed increased mortality in hospitalized patients randomized to tight control, the American College of Physicians recommends maintaining serum glucose between 140 mg/dL and 200 mg/dL (7.8–11.1 mmol/L), whereas the British National Health Service guidelines recommend a range of 108–180 mg/dL (6–10 mmol/L).

A. Diabetes Controlled by Diet

For people with diabetes controlled with diet alone, no special precautions must be taken unless diabetic control is markedly disturbed by the procedure. If this occurs, small doses of short-acting insulin as needed will correct the hyperglycemia.

B. Diabetes Treated with Oral Hypoglycemic Agents

Most oral hypoglycemic agents should be held on the day of surgery. However, the sodium-glucose transporter 2

inhibitors (eg, canagliflozin) should be held for 3–4 days before surgery due to their long half-life and associated risk of ketoacidosis. Oral hypoglycemic agents should not be restarted after surgery until patients are clinically stable and oral intake is adequate and unlikely to be interrupted. Patients who experience significant hyperglycemia when oral agents are held should be treated in the same way as patients with type 2 diabetes who require insulin, as described below. Postoperative kidney function should be checked with a serum creatinine level prior to restarting metformin.

C. Diabetes Treated with Insulin

The protocol used to control glucose depends on (1) the kind of diabetes (type 1 or type 2); (2) whether it is minor surgery (lasting less than 2 hours and patient able to eat afterward) or major surgery (lasting more than 2 hours, with invasion of a body cavity, and patient not able to eat afterward); and (3) the preoperative insulin regimen (basal bolus or premixed insulin twice a day or premeal bolus only or regular insulin before meals and NPH at bedtime).

1. Preoperative insulin regimen—For patients with either type 1 or type 2 diabetes who are receiving insulin, a common practice is to reduce the last preoperative dose of long-acting, basal insulin by 30–50% and hold short-acting nutritional insulin.

2. Perioperative insulin regimen—Patients with type 1 diabetes must receive basal insulin to prevent the development of diabetic ketoacidosis. **Consultation with an endocrinologist or hospitalist should be strongly considered when a patient with type 1 diabetes mellitus undergoes major surgery.** Major surgical procedures in patients with type 1 diabetes lasting more than 2 hours usually require an insulin infusion. Some patients with type 2 diabetes who are taking insulin will also need insulin infusion to maintain adequate glycemic control. An insulin infusion is a complex procedure for a high-risk medication and involves extensive monitoring, dose titrations, and contingency plans. There are a number of algorithms available for insulin infusions (http://ucsfinpatientdiabetes.pbworks.com).

3. Postoperative insulin regimen—After surgery, when a patient with either type 1 or type 2 diabetes has resumed adequate oral intake, subcutaneous administration of insulin can be restarted. Intravenous administration of insulin and dextrose can be stopped 30 minutes after the first subcutaneous dose. Insulin needs may vary in the first several days after surgery because of continuing postoperative stresses and because of variable caloric intake. In this situation, multiple doses of short-acting insulin plus some long-acting basal insulin, guided by blood glucose determinations, can keep the patient in acceptable metabolic control. Use of correctional insulin only (without basal or nutritional insulin) after surgery is discouraged. A trial comparing correctional insulin with basal-bolus dosing found that the latter strategy led to fewer postoperative complications.

Glucocorticoid Replacement

Hypotension or shock resulting from primary or secondary adrenocortical insufficiency is rare, and the practice of administering supraphysiologic "stress-dose" glucocorticoid perioperatively has not been well studied. A guideline from rheumatology and orthopedic surgery societies recommends that patients taking glucocorticoids continue their regimen when undergoing arthroplasty and not receive "stress-dose" glucocorticoids. Another approach is to administer stress-dose glucocorticoids to any patient who has received the equivalent of at least 7.5 mg of prednisone daily for 3 weeks within the past year when they undergo major surgery. A commonly used stress-dose regimen is hydrocortisone 100 mg intravenously daily, divided every 8 hours, beginning before induction of anesthesia and stopped after 24 hours without tapering. Patients who have been taking less than 5 mg of prednisone daily and those receiving alternate-day glucocorticoid dosing are unlikely to require supplemental coverage.

Thyroid Disease

Severe symptomatic hypothyroidism has been associated with perioperative complications, including intraoperative hypotension, HF, cardiac arrest, and death. Elective surgery should be delayed in patients with severe hypothyroidism until adequate thyroid hormone replacement can be achieved. Patients with symptomatic hyperthyroidism are at risk for perioperative thyroid storm and should not undergo elective surgery until their thyrotoxicosis is controlled; an endocrinologist should be consulted if emergency surgery is needed. Patients with mild hypothyroidism (median TSH level 8.6 mIU/L) tolerate surgery well, with only a slight increase in the incidence of intraoperative hypotension; surgery need not be delayed for the month or more required to ensure adequate thyroid hormone replacement.

Chilkoti GT et al. Perioperative "stress dose" of corticosteroid: pharmacological and clinical perspective. J Anaesthesiol Clin Pharmacol. 2019;35:147. [PMID: 31303699]
Preiser JC et al. Perioperative management of oral glucose-lowering drugs in the patient with type 2 diabetes. Anesthesiology. 2020;133:430. [PMID: 32667156]
Simha V et al. Perioperative glucose control in patients with diabetes undergoing elective surgery. JAMA. 2019;321:399. [PMID: 30615031]

KIDNEY DISEASE

The development of AKI in patients undergoing general surgery is an independent predictor of mortality, even if mild or if kidney dysfunction resolves. The mortality associated with the development of perioperative AKI that requires dialysis exceeds 50%. Risk factors associated with postoperative deterioration in kidney function are shown in Table 3–7. Several medications, including "renal-dose" dopamine, mannitol, *N*-acetylcysteine, and clonidine, have not been proved effective in clinical trials to preserve kidney function during the perioperative period and should not be used for this indication. **Maintenance of adequate intravascular volume is likely to be the most effective**

Table 3–7. Risk factors for the development of AKI after general surgery.[1]

Age > 55 years
Male sex
CKD
Heart failure
Diabetes mellitus
Hypertension
Ascites
Intraperitoneal surgery
Emergency surgery

[1]Presence of 5 or more risk factors is associated with > 3% risk of creatinine elevation > 2 mg/dL (176.8 mcmol/L) above baseline or requirement for dialysis.
Reproduced with permission from Kheterpal S et al, Development and Validation of an Acute Kidney Injury Risk Index for Patients Undergoing General Surgery: Results from a National Data Set, Anesthesiology, 2009;110(3): 505–15. https://pubs.asahq.org/anesthesiology/article/110/3/505/10107/Development-and-Validation-of-an-Acute-Kidney.

method to reduce the risk of perioperative deterioration in kidney function. Exposure to renal-toxic agents, such as NSAIDs and intravenous contrast, should be minimized or avoided. ACE inhibitors and ARBs reduce renal perfusion and may increase the risk of perioperative AKI. Although firm evidence is lacking, it may be useful to temporarily discontinue these medications in patients at risk for perioperative AKI.

Although the mortality rate for elective major surgery is low (1–4%) in patients with dialysis-dependent CKD, the risk for perioperative complications, including postoperative hyperkalemia, pneumonia, fluid overload, and bleeding, is substantially increased. Patients should undergo dialysis preoperatively within 24 hours before surgery, and their serum electrolyte levels should be measured just prior to surgery and monitored closely during the postoperative period.

Gumbert SD et al. Perioperative acute kidney injury. Anesthesiology. 2020;132:180. [PMID: 31687986]

ANTIBIOTIC PROPHYLAXIS OF SURGICAL SITE INFECTIONS

Surgical site infection is estimated to occur in roughly 4% of general or vascular operations. Although the type of procedure is the main factor determining the risk of developing a surgical site infection, certain patient factors have been associated with increased risk, including diabetes mellitus, older age, obesity, smoking, heavy alcohol consumption, admission from a long-term care facility, and multiple medical comorbidities. **For most major procedures, the use of prophylactic antibiotics has been demonstrated to reduce the incidence of surgical site infections.** Substantial evidence suggests that a single dose of an appropriate intravenous antibiotic—or combination of antibiotics—administered 30–60 minutes prior to skin incision is as effective as multiple-dose regimens that extend into the postoperative period. For most procedures, a first-generation cephalosporin (eg, cefazolin 2 g intravenously) is as effective as later-generation agents.

Guidelines for antibiotic prophylaxis against infective endocarditis in patients undergoing invasive procedures are presented in Chapter 33. Given the lack of evidence for antibiotic prophylaxis against prosthetic joint infection before dental procedures, guidelines from the American Academy of Orthopedic Surgeons and the American Dental Association recommend against this practice.

Fields AC et al. Preventing surgical site infections: looking beyond the current guidelines. JAMA. 2020;323:1087. [PMID: 32083641]

4 Geriatric Disorders

Leah J. Witt, MD
Rossana Lau-Ng, MD
G. Michael Harper, MD

GENERAL PRINCIPLES OF GERIATRIC CARE

The following principles help in caring for older adults:

1. Many disorders are multifactorial in origin and are best managed by multifactorial interventions.
2. Diseases often present atypically or with nonspecific symptoms (eg, confusion, functional decline).
3. Not all abnormalities require evaluation and treatment.
4. Complex medication regimens, adherence problems, and polypharmacy are common challenges.
5. Multiple chronic conditions often coexist and should be managed in concert with one another.

COMPREHENSIVE ASSESSMENT OF THE OLDER ADULT

In addition to conventional assessment of symptoms, diseases, and medications, comprehensive assessment addresses three topics: **prognosis, values and preferences**, and **ability to function independently.** Comprehensive assessment is warranted before major clinical decisions are made.

Assessment of Prognosis

When an older person's life expectancy is longer than 10 years (ie, 50% of similar persons live longer than 10 years), it is reasonable to consider effective tests and treatments much as they are considered in younger persons. When life expectancy is less than 10 years (and especially when it is much less), choices of tests and treatments should be made based on their ability to affect a clinical outcome that is valued by the patient in the context of their estimated life expectancy. The relative benefits and harms of tests and treatments often change as prognosis worsens, and net benefit (benefits minus harms) often worsens.

When an older patient's clinical situation is dominated by a single disease process (eg, lung cancer metastatic to brain), prognosis can be estimated well with a disease-specific instrument. Even in this situation, however, prognosis generally worsens with age (especially over age 90 years) and with the presence of serious age-related conditions, such as dementia, malnutrition, or functional impairment.

When an older patient's clinical situation is not dominated by a single disease process, prognosis can be estimated initially by considering basic demographic and health elements (Figure 4–1). For example, less than 25% of men aged 95 will live 5 years, whereas nearly 75% of women aged 70 will live 10 years. The prognosis for older persons living at home can be estimated by considering age, sex, comorbid conditions, and function. The prognosis is worse for older persons discharged from the hospital than for those living at home and can be estimated by considering sex, comorbid conditions, and function at discharge. A compilation of indices with online calculators that allow for estimating prognosis in multiple clinical settings can be found at ePrognosis (https://eprognosis.ucsf.edu).

Assessment of Values & Preferences

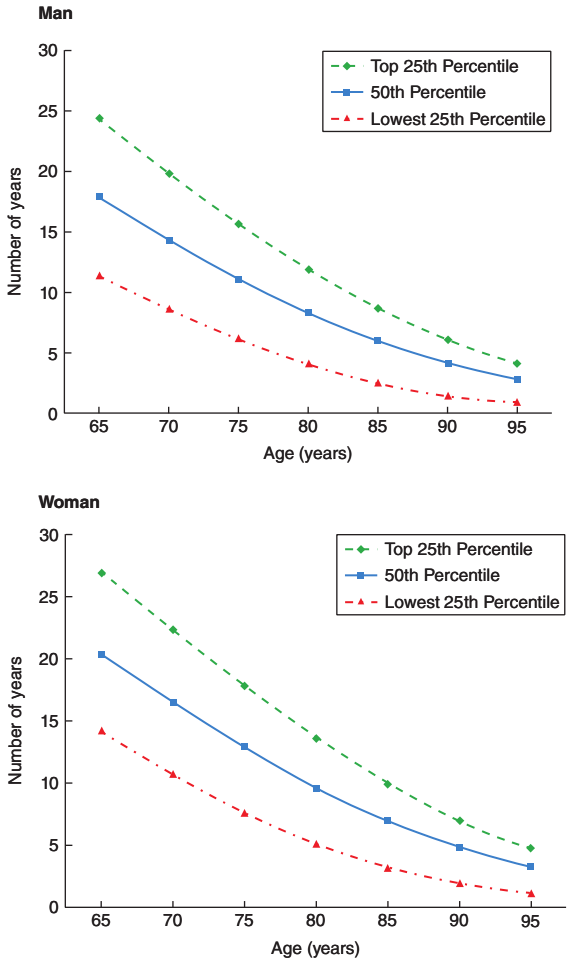
Although patients vary in their values and preferences, many frail older patients prioritize maintaining their independence over prolonging survival. Values and preferences are determined by speaking directly with a patient or, when the patient cannot express preferences reliably, with the patient's surrogate.

In assessing values and preferences (ie, what matters most to patients), it is important to keep in mind the following:

1. Patients are experts about their preferences for outcomes and experiences; however, they may not have adequate information to make and express informed preferences for specific tests or treatments.
2. Patients' preferences often change over time. For example, some patients find living with a disability more acceptable than they thought before experiencing it.

Assessment of Function

People often lose function in multiple domains as they age, with the result that they may not be able to do some activities as quickly or capably and may need assistance. Assessment of function improves prognostic estimates.



▲ **Figure 4–1.** Median life expectancy of older men and women. (Data derived from Arias E. United States Life Tables, 2011. Natl Vital Stat Rep. 2015;64(11):1–63.)

Assessment of function is essential to determine an individual's needs in the context of his or her values and preferences and the possible effects of recommended treatment.

About one-fourth of patients over age 65 and half of persons older than 85 need help performing their **basic activities of daily living (ADLs:** bathing, dressing, eating, transferring from bed to chair, continence, toileting) or **instrumental activities of daily living (IADLs:** transportation, shopping, cooking, using the telephone, managing money, taking medications, housecleaning, laundry).

Functional screening should include assessment of ADLs and IADLs and questions to detect weight loss, falls, incontinence, depressed mood, self-neglect, fear for personal safety, and common serious impairments (eg, hearing, vision, cognition, and mobility). Standard functional screening measures may not be useful in capturing subtle impairments in highly functional independent older adults. One technique for these patients is to identify and ask about a target routine activity, such as bowling or gardening. Difficulty with or discontinuation of the particular activity may indicate new or worsening impairment (such as cognitive impairment, urinary incontinence, or hearing loss). Additional gentle questioning or assessment may help uncover such changes.

Frailty

Frailty is a syndrome characterized by loss of physiologic reserve and dysregulation across multiple systems, ultimately resulting in greater risk of poor health outcomes. Estimates of its prevalence in community-dwelling older adults range from 5% to 17%. Elements of frailty include **weakness (grip strength), slow gait speed, decreased physical activity, weight loss,** and **exhaustion or low energy.** While there is not one universally agreed upon definition or assessment tool for frailty, generally an individual is defined as frail when three or more of the above features are present. Persons with frailty are at increased risk for falls, hospitalization, functional decline, poorer outcomes associated with medical interventions (eg, surgery, dialysis, chemotherapy), and death. **Exercise, particularly strength and resistance training, can increase walking speed and improve function.** There is evidence that optimal nutrition, particularly higher levels of protein intake, may be associated with reduced incidence of frailty. However, once frailty is established, the treatment is largely supportive, multifactorial, and individualized based on patient goals, life expectancy, and chronic conditions. Sometimes, transitioning a patient to a comfort-focused or hospice approach is the most appropriate clinical intervention when irreversible complications from frailty develop.

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Pilotto A et al. A multidimensional approach to frailty in older people. Ageing Res Rev. 2020;60:101047. [PMID: 32171786]

MANAGEMENT OF COMMON GERIATRIC PROBLEMS

1. Dementia

ESSENTIALS OF DIAGNOSIS

- Progressive decline of mental processes.
- Acquired cognitive deficits severe enough to impair function.
- Not due to delirium or another mental disorder.

General Considerations

Dementia is an acquired, persistent, and progressive impairment in mental processes, with compromise of one or more cognitive domains. *The Diagnostic and Statistical Manual of Mental Disorders,* 5th edition, identifies these domains (with example deficits) as: (1) **complex attention**

(easily distracted, difficulty performing calculations), (2) **executive function** (poor abstraction, mental flexibility, planning, and judgment), (3) **learning and memory** (difficulty recalling items from a list, forgetting recent events), (4) **language** (word finding and object naming difficulty), (5) **perceptual-motor function** (difficulty navigating in known environments, copying a drawing), and (6) **social cognition** (change in personality, trouble reading social cues). The diagnosis of dementia requires a significant decline in function that is *severe enough to result in the loss of independence in IADLs.*

While dementia prevalence doubles every 5 years in the older population, reaching 30–50% at age 85, the prevalence among US adults 65 years or older has been declining. This improvement has been attributed to higher education levels and better control of cardiovascular risk factors. Alzheimer disease accounts for roughly two-thirds of dementia cases in the United States, with vascular dementia (either alone or combined with Alzheimer disease) and Lewy body dementia accounting for much of the rest.

Depression and delirium are also common in older adults, may coexist with dementia, and may also present with cognitive impairment. Major depressive disorder may occur in up to 20–50% of patients with dementia, and because they share common features, distinguishing the two can prove difficult. Delirium, characterized by acute confusion, occurs much more commonly in patients with underlying dementia.

Clinical Findings

A. Screening

1. Cognitive impairment—According to the USPSTF, there is insufficient evidence to recommend for or against screening all older adults for cognitive impairment. While there is logic in the argument that early detection may improve future planning and patient outcomes, empiric evidence that demonstrates a clear benefit for either patients or caregivers is lacking. It is important to note, however, that the Medicare Annual Wellness Visit mandates that clinicians assess patients for cognitive impairment based on the clinician's observations and reports from others.

At-home genetic testing for a susceptibility gene that is associated with late-onset Alzheimer disease (APOE-e4) has US FDA approval. While the presence of the APOE-e4 allele increases the risk of developing Alzheimer disease, quantifying such risk for an individual is difficult. Because it is possible to have one or two copies of the APOE-e4 allele and not develop Alzheimer disease or to have no copies and yet still become stricken, genetic testing is not widely recommended and, if considered, should not proceed without genetic counseling.

When there is suspicion of cognitive impairment, several cognitive tests have been validated for clinical use. The **mini-cog** is a combination of a three-item word recall with a clock drawing task, and it can be completed in 3 minutes. When a patient fails this simple test, further cognitive evaluation with a standardized instrument is warranted. The **Montreal Cognitive Assessment (MoCA©)** is a 30-point test that takes about 10 minutes to administer and examines several areas of cognitive function. A score below 26 has a sensitivity of 0.94 or more and a specificity of 0.60 or less. Free downloadable versions in multiple languages are available at https://www.mocatest.org. Completion of a training and certification program or signing a disclaimer if you choose not to take the training is required to gain access to the test.

2. Decision-making capacity—Older adults with cognitive impairment commonly face serious medical decisions, and the clinicians involved in their care must ascertain whether the capacity exists to make medical decisions. While no single test of capacity exists, the following five elements should be considered in a thorough assessment: (1) ability to express a choice; (2) understanding relevant information about the risks and benefits of the proposed intervention and the alternatives (including no intervention), in the context of one's values; (3) comprehension of the problem and its consequences; (4) ability to reason; and (5) consistency of choice. A patient's choice should follow from an understanding of the consequences.

Sensitivity must be used in applying these five components to people of various cultural backgrounds. Decision-making capacity varies over time. Furthermore, the capacity to make a decision is a function of the decision in question.

B. Symptoms and Signs

Most patients with dementia can be identified in a primary care setting after completion of a history (often requiring collateral information), a physical examination, and cognitive testing. The clinician can gather additional information about the type of dementia by asking about (1) the rate of progression of the deficits as well as their nature (including any personality or behavioral change); (2) the presence of other neurologic and psychiatric symptoms, particularly motor problems and psychotic symptoms; (3) risk factors for HIV; (4) family history of dementia; and (5) medications, with particular attention to recent changes.

Workup is directed at identifying any potentially *reversible* causes of dementia. However, such cases are rare. For a detailed description of the symptoms and signs of different forms of dementia, see Chapter 24.

C. Physical Examination

The neurologic examination emphasizes assessment of mental status but should also include evaluation for sensory deficits, previous strokes, parkinsonism, gait impairment, and peripheral neuropathy. The examination should focus on identifying comorbid conditions that may aggravate the individual's disability. For a detailed description of the neuropsychological assessment, see Chapter 24.

D. Laboratory Findings

Laboratory studies should include a CBC and serum electrolytes, calcium, creatinine, glucose, TSH, and vitamin B_{12} levels. While hypothyroidism or vitamin B_{12} deficiency may contribute to the cognitive impairment,

treating these conditions typically does *not* reverse the dementia. HIV and rapid plasma reagin (RPR) tests, a heavy metal screen, and liver biochemical tests may be informative in selected patients but are not part of routine testing. For a detailed description of laboratory findings, see Chapter 24.

E. Imaging

The American Academy of Neurology recommends neuroimaging (noncontrast head CT or MRI) in all patients with dementia while other experts limit routine use of neuroimaging to those patients more likely to have a structural cause of dementia (eg, subdural hematoma, tumor, previous stroke, and hydrocephalus). Those who are younger; those who have focal neurologic symptoms or signs, seizures, or gait abnormalities; and those with an acute or subacute onset are most likely to have positive findings and most likely to benefit from MRI scanning. In older patients with a more classic picture of Alzheimer disease for whom neuroimaging is considered, a noncontrast CT scan is sufficient. For a detailed description of imaging, see Chapter 24.

Differential Diagnosis

Older individuals experience occasional difficulty retrieving items from memory (usually word-finding difficulty) and experience a slowing in their rate of information processing. In the amnestic type of **mild cognitive impairment (MCI)**, a patient complains of memory problems, demonstrates mild deficits (most commonly in short-term memory) on formal testing, but the impairment does not significantly impact function. Annual dementia conversion rates vary from less than 5% to 20%. No medications have been demonstrated to delay the progression of MCI to Alzheimer disease. An elderly patient with intact cognition but with severe impairments in vision or hearing may become confused in an unfamiliar medical setting and consequently may be falsely labeled as having dementia.

Delirium can be distinguished from dementia by its acute onset, fluctuating course, and deficits in attention rather than memory. Many medications have been associated with delirium and other types of cognitive impairment in older patients. Anticholinergic agents, hypnotics, neuroleptics, opioids, NSAIDs, antihistamines (both H_1- and H_2-antagonists), and corticosteroids are just some of the medications that have been associated with cognitive impairment in elders.

Treatment

Patients and families should be made aware of the Alzheimer's Association (http://www.alz.org) as well as the wealth of helpful community and online resources and publications available. Caregiver support, education, and counseling may prevent or delay nursing home placement. Education should include the manifestations and natural history of dementia as well as the availability of local support services, such as respite care. Exercise should be a component of treatment as evidence suggests physical activity may have beneficial effects on cognition and physical function.

A. Cognitive Impairment

1. Acetylcholinesterase inhibitors—Donepezil, galantamine, and rivastigmine are acetylcholinesterase inhibitors approved for the treatment of Alzheimer disease. These medications produce a modest improvement in cognitive function that is *not* likely to be detected in routine clinical encounters, and they have *not* convincingly been shown to delay functional decline or institutionalization. There is insufficient evidence to recommend their use in MCI to slow the progression toward dementia.

Starting (and maximum) doses are donepezil, 5 mg orally once daily (maximum 10 mg once daily); galantamine, 4 mg orally twice daily (maximum 12 mg twice daily); extended-release galantamine, 8 mg orally once daily (maximum 24 mg once daily); rivastigmine, 1.5 mg orally twice daily (maximum 6 mg twice daily); and rivastigmine transdermal patch, 4.6 mg/24 h (maximum 13.3 mg/24 h for severe disease). Dosages are increased as tolerated at no less than 4-week intervals. Donepezil is also available in a 23-mg tablet, but this higher dose is associated with greater frequency of side effects without appreciable increase in benefit. The most bothersome side effects of acetylcholinesterase inhibitors include diarrhea, nausea, anorexia, weight loss, and syncope. As dementia progresses, some patients with moderate to severe cognitive impairment may continue to experience subjective benefits from acetylcholinesterase inhibitors, but the medication should be discontinued in those patients who have had no apparent benefit, who experience side effects, or for whom the financial outlay is a burden. While there are no published guidelines that describe what constitutes an adequate treatment trial, evaluation after 2 months at the highest tolerated dose is reasonable.

2. Memantine—In clinical trials, patients with moderate to severe Alzheimer disease have been shown to have statistical benefit from the use of memantine (5 mg orally daily to 10 mg twice daily), an *N*-methyl-D-aspartate (NMDA) antagonist. Long-term and meaningful functional outcomes have yet to be demonstrated, and evidence suggests there is no clinically meaningful benefit to giving memantine in combination with an acetylcholinesterase inhibitor. Evidence does not support the use of memantine in other forms of dementia.

3. Aducanumab—In 2021, the FDA approved aducanumab, a monoclonal antibody that targets amyloid-beta protein and promotes its clearance from the brain, for the treatment of Alzheimer disease. Its approval was based mainly on the results of two identical phase 3 randomized clinical trials sponsored by the drug's manufacturer (ENGAGE and EMERGE) that enrolled participants aged 50–85 years with either MCI or early Alzheimer disease and amyloid-beta positive PET scans. Participants were randomized to either low- or high-dose aducanumab or placebo. The primary end point was the change in the mean score on the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) at 18 months. Both studies were terminated early when they met prespecified criteria for futility. However, further data analysis of the high-dose arm in the EMERGE trial identified a statistically significant change

in the CDR-SB score, but the difference was smaller than what would be considered clinically meaningful. Both studies found significant reduction in amyloid-beta plaque on PET imaging compared to placebo and yet the reasons for the divergent clinical outcomes are largely unexplained.

Roughly 40% of patients who received high-dose aducanumab in the two trials experienced amyloid-related imaging abnormalities, a known class effect of these drugs. While most cases were asymptomatic, about 25% experienced symptoms, such as headaches, confusion, or dizziness; these symptoms usually resolved with dose reduction or stopping the drug. The overall discontinuation rate in the high-dose group was 6.2% compared to 0.6% in the placebo group.

Before receiving approval, the FDA's scientific advisory panel voted nearly unanimously in recommending against aducanumab's approval, citing the lack of sufficient evidence demonstrating that it slowed cognitive decline. At an annual cost of $56,000 per year, aducanumab requires monthly intravenous infusions. Aducanumab should be restricted to patients with MCI or mild Alzheimer disease who demonstrate amyloid-beta protein on PET imaging and who can be monitored frequently for potential adverse effects.

B. Behavioral Problems

1. Nonpharmacologic approaches—Behavioral problems in patients with dementia are often best managed nonpharmacologically. Initially, it should be established that the problem is not unrecognized delirium, pain, urinary obstruction, or fecal impaction. Determining whether the caregiver or institutional staff can tolerate the behavior is also helpful, since it is often easier to find ways to accommodate to the behavior than to modify it. If not, the caregiver should keep a brief log in which the behavior is described along with antecedent events and consequences. This may uncover patterns that delineate precipitants of the behavior or perhaps that the behavior is somehow being rewarded. Caregivers are taught to use simple language when communicating with the patient, to break down activities into simple component tasks, and to use a "distract, not confront" approach when the patient seems disturbed by a troublesome issue. Additional steps to address behavioral problems include providing structure and routine, discontinuing all medications except those considered absolutely necessary, and correcting, if possible, sensory deficits.

2. Pharmacologic approaches—There is no clear consensus about pharmacologic approaches to the treatment of behavioral problems in patients who have not benefited from nonpharmacologic therapies. Pharmacologic treatment should be reserved for those patients who pose an imminent danger to others or themselves or when symptoms are substantially distressing to the patient.

Despite evidence of harm and recommendations against their use, antipsychotic medications have remained a mainstay for the treatment of behavioral disturbances, particularly agitation and aggression, largely because of the lack of alternatives. The atypical antipsychotic agents (eg, risperidone, olanzapine, quetiapine, aripiprazole) are increasingly becoming the first choice because of an overall better side-effect profile compared to typical agents (eg, haloperidol) but should be used with caution in patients with vascular risk factors due to an increased risk of stroke; they can also cause weight gain and are also associated with hyperglycemia in diabetic patients and are considerably more expensive. Both typical and atypical antipsychotics increase mortality compared with placebo when used to treat elderly patients with dementia and behavioral disturbances. Starting and target dosages should be much lower than those used in schizophrenia (eg, haloperidol, 0.5–2 mg orally; risperidone, 0.25–2 mg orally).

Citalopram at a dose of 30 mg daily may improve symptoms of agitation; however, according to the US FDA, the maximum recommended dose is 20 mg daily for patients older than 60 years because of the risk of QT prolongation and associated dysrhythmia. Thus, while citalopram may be used to treat agitation, safe and effective dosing for patients older than age 60 has not been established. In the specific instance of patients with Lewy body dementia, treatment with acetylcholinesterase inhibitors has been shown to improve behavioral symptoms. Valproate medications have been used in the treatment of agitated and physically aggressive behavior, but evidence demonstrates no identifiable benefit.

C. Driving

Although drivers with dementia are at an increased risk for motor vehicle accidents, many patients continue to drive safely well beyond the time of initial diagnosis, making the timing of when to recommend that a patient stop driving particularly challenging.

There is no clear-cut evidence to suggest a single best approach to determining an individual patient's capability, and there is no accepted "gold-standard" test. The result is that clinicians must consider several factors upon which to base their judgment. For example, determining the severity of dementia can be useful. Patients with very mild or mild dementia according to the Clinical Dementia Rating Scale were able to pass formal road tests at rates of 88% and 69%, respectively. Experts agree that patients with moderately severe or more advanced dementia should be counseled to stop driving. Although not well studied, clinicians should also consider the effects of comorbid conditions and medications and the role each may play in contributing to the risk of driving by a patient with dementia. Assessment of the ability to carry out IADLs may also assist in the determination of risk. Finally, in some cases of mild dementia, referral may be needed to a driver rehabilitation specialist for evaluation. Although not standardized, this evaluation often consists of both off- and on-road testing. Experts recommend such an evaluation for patients with mild dementia, for those with dementia for whom new impairment in driving skills is observed, and for those with significant deficits in cognitive domains, such as attention, executive function, and visuospatial skills.

Clinicians must also be aware of the reporting requirements in their individual jurisdictions. When a clinician has made the decision to report an unsafe driver to the Department of Motor Vehicles, he or she must consider the impact of a potential breach in confidentiality and must

weigh and address, in advance when possible, the consequences of the loss of driving independence.

D. Advance Financial Planning

Difficulty in managing financial affairs often develops early in the course of dementia. Although expertise is not expected, clinicians should have some proficiency to address financial concerns. Just as clinicians counsel patients and families about advance care planning, the same should be done to educate about the need for advance financial planning and to recommend that patients complete a **durable power of attorney for finance matters (DPOAF)** while the capacity to do so still exists.

No gold-standard test is available to identify when a patient with dementia no longer has financial capacity. However, the clinician should be on the lookout for signs that a patient is either at risk for or actually experiencing financial incapacity. Because financial impairment can occur when dementia is mild, making that diagnosis should alone be enough to warrant further investigation. Questioning patients and caregivers about late, missed, or repeated bill payments, unusual or uncharacteristic purchases or gifts, overdrawn bank accounts, or reports of missing funds can provide evidence of suspected financial impairment. Patients with dementia are also at increased risk for becoming victims of financial abuse, and some answers to these same questions might also be signs of potential exploitation. When financial abuse is suspected, clinicians should be aware of the reporting requirements in their local jurisdictions.

Prognosis

Life expectancy after a diagnosis of Alzheimer disease is typically 3–15 years; it may be shorter than previously reported. Other neurodegenerative dementias, such as Lewy body dementia, show more rapid decline. Hospice care is often appropriate for patients with end-stage dementia.

When to Refer

Referral for neuropsychological testing may be helpful to distinguish dementia from depression, to diagnose dementia in persons of very poor education or very high premorbid intellect, and to aid diagnosis when impairment is mild.

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Smith EE et al. Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD)5: guidelines for management of vascular cognitive impairment. Alzheimers Dement (N Y). 2020;6:e12056. [PMID: 33209971]

Tung EE et al. Approach to the older adult with new cognitive symptoms. Mayo Clin Proc. 2020;95:1281. [PMID: 32498781]

Zhuang L et al. Cognitive assessment tools for mild cognitive impairment screening. J Neurol. 2021;268:1615. [PMID: 31414193]

2. Depression

ESSENTIALS OF DIAGNOSIS

- May manifest in older adults as physical complaints (eg, fatigue, anhedonia) rather than complaints of depressed mood.
- Often undertreated in older adults. Approximately one-third of those treated with an antidepressant will achieve remission, and two-thirds will need additional treatment.

General Considerations

Major depressive disorder has prevalence rates of approximately 2% among community-dwelling adults aged 55 years and older. Prevalence rises with increasing age as well as conditions such as chronic illness, multimorbidity, cognitive impairment, and functional impairment. Major depressive disorder is less common in older adults than younger adults, but *depressive symptoms* (not meeting criteria for major depressive disorder) are common and present in up to 15% of older adults. Depression is more common among hospitalized and institutionalized elders. Older single men have the highest rate of completed suicides of any demographic group.

New incidence of depressive symptoms may be an early sign of cognitive impairment in older adults; therefore, evaluation of depression should include cognitive assessment. Older patients with depression and depressive symptoms who have comorbid conditions (eg, heart failure) are at higher risk for hospitalization, tend to have longer hospital stays, and have worse outcomes than patients without depression.

Clinical Findings

The **Patient Health Questionnaire-2 (PHQ-2)** is highly sensitive for detecting major depression in persons over age 65. Positive responses should be followed up with more comprehensive, structured interviews, such as the PHQ-9.

Evaluation of depression should include a careful review of substances that can contribute to depressive symptoms, such as medications (eg, benzodiazepines) and alcohol/illicit drugs. A thorough review of the medical history is critical, since many medical problems can cause fatigue, lethargy, or hypoactive delirium, all of which may be mistaken for depression.

Treatment

First-line treatment is the same for older adults as it is for younger adults; psychotherapy and SSRI medications are the mainstays of treatment. Adjunctive treatment may include psychosocial interventions, increased physical activity, reduction of substance use (eg, alcohol), reduction of potentially contributing medications, or electroconvulsive therapy. Depressed older adults may do better with a collaborative or multidisciplinary care model that includes socialization and other support elements. In older patients

with depressive symptoms who do not meet criteria for major depressive disorder, nonpharmacologic treatments are indicated. Telehealth for mental health support is an important innovation in the field.

Choice of antidepressant agent is usually based on side-effect profile, cost, and patient-specific factors, such as presenting symptoms and comorbidities. SSRIs are used as first-line agents because they are relatively well-tolerated and have good evidence to support efficacy (see Table 25–6). Older adults are more susceptible to SSRI-induced hyponatremia, falls, and osteoporosis. SNRIs (eg, duloxetine and venlafaxine) lead to more adverse events versus placebo than do SSRIs. Regardless of the medication chosen, many experts recommend starting elders at a relatively low dose, titrating to full dose slowly, and continuing for a longer trial (at least 8 weeks) before trying a different medication. Titration to full dose is critical to achieve efficacy of treatment. Of note, the maximum citalopram dose for adults older than 60 years is 20 mg orally daily, due to dose-dependent QT prolongation.

One-third of older adults achieve remission after adequate treatment with first-line SSRI treatment. For the remainder, referral to a mental health specialist is indicated. For those who do not achieve remission, augmentation therapy (eg, with lithium, methylphenidate, or aripiprazole) can enhance clinical response. Esketamine, the S-enantiomer of ketamine, is approved for treatment-resistant depression, but studies of its safety and efficacy did not include adults older than age 65. For patients with severe or catatonic depression, electroconvulsive therapy has high rates of efficacy (60–80%) and should be considered.

Pharmacologic treatment for the first episode of depression should continue for 1 year after remission. Clinicians and patients should share in decision-making regarding maintenance therapy for depression since risk of major depressive disorder recurrence is high. This decision should weigh how long-term pharmacotherapy may contribute to polypharmacy and adverse effects in the landscape of their patient's comorbidities and medication regimen.

When to Refer

- Any patient who might be considered for electroconvulsive therapy should be referred for psychiatric evaluation.
- Consider referral for patients who have mania, psychosis, catatonia, or treatment-resistant depression.

When to Admit

Consider psychiatric evaluation and admission for patients who have psychosis, suicidality, homicidality, catatonia, grave disability, or self-neglect.

Choi NG et al. Effect of telehealth treatment by lay counselors vs by clinicians on depressive symptoms among older adults who are homebound: a randomized clinical trial. JAMA Network Open. 2020;3:e2015648. [PMID: 32865577]

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Sobieraj DM et al. Adverse effects of pharmacologic treatments of major depression in older adults. J Am Geriatr Soc. 2019; 67:1571. [PMID: 31140587]

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3. Delirium

ESSENTIALS OF DIAGNOSIS

- Rapid onset and fluctuating course.
- Primary deficit in attention rather than memory.
- May be hypoactive or hyperactive.
- Dementia frequently coexists.

General Considerations

Delirium is an acute, fluctuating disturbance of consciousness, associated with a change in cognition or development of perceptual disturbances (see also Chapter 25). It is the pathophysiologic consequence of an underlying general medical condition, such as infection, coronary ischemia, hypoxemia, or metabolic derangement. Delirium occurs in 29–64% of hospitalized older adults, persists in 25% or more, and is associated with worse clinical outcomes (higher in-hospital and post-discharge mortality, longer lengths of stay, delayed and limited recovery of physical function, greater probability of placement in a nursing facility).

Although the acutely agitated elderly patient often comes to mind when considering delirium **(hyperactive delirium),** many episodes are subtler. Such **hypoactive delirium** may be suspected only if one notices new cognitive slowing or inattention.

Cognitive impairment is an important risk factor for delirium. Other risk factors include severe illness, polypharmacy, use of psychoactive medications, sensory impairment, depression, and alcoholism.

Clinical Findings

Several bedside instruments are available for the assessment of delirium (http://www.hospitalelderlifeprogram.org/delirium-instruments/). The **confusion assessment method (CAM)** requires (1) acute onset and fluctuating course and (2) inattention and *either* (3) disorganized thinking *or* (4) altered level of consciousness. The 3D CAM (3-minute diagnostic CAM) is particularly useful for clinical assessment of delirium.

A key component of a delirium workup is review of medications because polypharmacy, the addition of a new medication, an increase in dose of a medication, or the discontinuation of a medication known to cause withdrawal symptoms are all associated with the development

of delirium. Medications that are particularly likely to increase the risk of delirium include sedative/hypnotics, anticholinergics, opioids, benzodiazepines, and H_1- and H_2-antihistamines.

Evaluation of most patients should include a CBC; BUN; serum electrolytes, creatinine, glucose, calcium, albumin, and liver biochemical tests; UA; and ECG. In selected cases, serum magnesium, medication levels, arterial blood gas measurements, blood cultures, chest radiography, urinary toxin screen, and lumbar puncture may be helpful. When delirium develops during a hospitalization in the absence of trauma or new localizing neurologic signs, a head CT is rarely revealing.

Prevention

The best evidence for prevention comes from nonpharmacologic multicomponent interventions. These components include improving cognition (frequent reorientation, activities, socialization with family and friends when possible), sleep (massage, noise reduction, minimizing interruptions at night), mobility (early initiation of rehabilitation services as appropriate), vision (visual aids and adaptive equipment), hearing (portable amplifiers or hearing aids, cerumen disimpaction), and hydration status (volume repletion). No medications, including antipsychotics, have been consistently shown to prevent delirium or improve outcomes such as length of stay or mortality should delirium develop.

Treatment

Management of established episodes of delirium combines the elements of preventive interventions with reassurance and reorientation, treatment of underlying causes, eliminating unnecessary medications, and avoidance of indwelling catheters and restraints. Antipsychotics, while still a mainstay of delirium treatment in hospitalized adults, offer little to no proven benefit and can cause harm. For example, haloperidol and second-generation antipsychotics have not been found to reduce delirium severity or duration, hospital length of stay, or mortality when compared to placebo. QT interval prolongation can occur and is a potential risk for serious dysrhythmias. Benzodiazepines should be avoided except in the circumstance of alcohol or benzodiazepine withdrawal. In ventilated patients in the ICU setting, dexmedetomidine or propofol (or both) may also be useful alternatives to antipsychotic therapy in patients with delirium.

Most episodes of delirium clear in a matter of days after correction of the precipitant, but some patients suffer episodes of much longer duration, and a significant percentage never return to their former baseline level of functioning.

When to Refer

If an initial evaluation does not reveal the cause of delirium or if entities other than delirium are in the differential diagnosis, referral to a geriatrician, neuropsychologist, neurologist, or geropsychiatrist should be considered.

When to Admit

Patients with delirium of unknown cause should be admitted for an expedited workup if consistent with the patient's goals of care.

Hshieh TT et al. Delirium in the elderly. Clin Geriatr Med. 2020;36:183. [PMID: 32222295]

Inouye SK. The importance of delirium and delirium prevention in older adults during lockdowns. JAMA. 2021;325:1779. [PMID: 33720288]

Kotfis K et al. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. Crit Care. 2020;24:176. [PMID: 32345343]

Pereira JV et al. Delirium in older adults is associated with development of new dementia: a systematic review and meta-analysis. Int J Geriatr Psychiatry. 2021;36:993. [PMID: 33638566]

Salvi F et al. Non-pharmacological approaches in the prevention of delirium. Eur Geriatr Med. 2020;11:71. [PMID: 32297241]

4. Immobility

Mobility limitations are common in older adults and are associated with increased rates of morbidity, hospitalization, disability, and mortality. Hospital-associated bed rest is a common precipitant of immobility and functional decline. Among hospitalized medical patients over age 70, about 10% experience a decline in function, and those who experience critical illness are particularly at high risk.

The hazards of bed rest in older adults are multiple, serious, quick to develop, and slow to reverse. Within days of being confined to bed, deconditioning of the cardiovascular system occurs. This deconditioning causes fluid shifts, decreased cardiac output, decreased peak oxygen uptake, increased resting heart rate, and postural hypotension. More striking changes occur in skeletal muscle, resulting in loss of strength and function. Pressure injuries, venous thromboembolism, and falls are additional serious outcomes of immobility and deconditioning.

Prevention & Treatment

Physical activity should be encouraged for all elders, particularly sedentary elders. Physical activity is associated with a myriad of health benefits in older adults. Structured physical activity programs may help reduce mobility-related disability among community-dwelling elders.

When immobilization cannot be avoided, several measures can be used to minimize its consequences. To reduce the risks of contracture and weakness, range-of-motion and strengthening exercises should be started immediately and continued as long as the patient is in bed. Avoiding restraints and discontinuing intravenous lines and urinary catheters will increase opportunities for early mobility. Graduated ambulation should begin as soon as it is feasible. Among hospitalized elders, exercise protocols can improve functional outcomes. Prior to discharge, physical therapists can recommend appropriate exercises and assistive devices; after discharge, they can recommend home safety modifications and maintenance exercises. Severe functional disability impeding the ability to care for oneself independently often leads to discharge to an acute or subacute rehabilitation

facility. Recovery from illness-related deconditioning takes weeks to months, and in many cases, full recovery to the pre-illness physical condition does not occur.

Flint LA et al. Rehabbed to death. N Engl J Med. 2019;380:408. [PMID: 30699322]
Martínez-Velilla N et al. Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: a randomized clinical trial. JAMA Intern Med. 2019;179:28. [PMID: 30419096]
Pahor M et al. Impact and lessons from the Lifestyle Interventions and Independence for Elders (LIFE) clinical trials of physical activity to prevent mobility disability. J Am Geriatr Soc. 2020;68:872. [PMID: 32105353]

5. Falls & Gait Disorders

Annually, about one-third of people over age 65 fall, and the frequency of falls increases markedly with advancing age. About 10% of falls result in serious injuries. Complications from falls (eg, hip fracture, subdural hematoma) are the leading cause of death from injury in persons over age 65, and fall-associated mortality is increasing.

Every older person should be asked about falls. Assessment of patients who fall should include postural blood pressure and pulse; cardiac examination; evaluations of strength, range of motion, cognition, and proprioception; and examination of feet and footwear. A thorough gait assessment should be performed in all older people. Gait and balance can be readily assessed by the **"Timed Up and Go Test,"** in which the patient is asked to stand up from a sitting position without use of hands, walk 10 feet/3 meters, turn around, walk back, and sit down. An older adult who takes 12.5 seconds or greater is considered at increased risk for falling. The ability to recognize common patterns of gait disorders is an extremely useful clinical skill to develop. Examples of gait abnormalities and their causes are listed in Table 4–1.

Causes of Falls

Balance and ambulation require a complex interplay of cognitive, neuromuscular, and cardiovascular function. With age, balance mechanisms can become compromised, reaction time slows, and postural sway increases. These changes predispose the older person to a fall when challenged by an additional insult to any of these systems.

Falls in older people are rarely due to a single cause, and effective intervention entails a comprehensive assessment of the patient's intrinsic deficits (eg, diseases and medications), the activity engaged in at the time of the fall, and environmental obstacles (Table 4–2).

Intrinsic deficits are those that impair sensory input, judgment, blood pressure regulation, reaction time, and balance and gait. Dizziness may be closely related to the deficits associated with falls and gait abnormalities. While it may be impossible to isolate a sole cause or a "cure" for falls, gait abnormalities, or dizziness, it is often possible to identify and ameliorate some of the underlying contributory conditions and improve the patient's overall function.

Medication use is one of the most common, significant, and reversible causes of falling. A meta-analysis found that sedative/hypnotics, antidepressants, and benzodiazepines were the classes of medications most likely to be associated with falling. The use of multiple medications simultaneously has also been associated with increased fall risk. Other often overlooked but treatable contributors include postural hypotension (including postprandial, which peaks 30–60 minutes after a meal), insomnia, use of multifocal lenses, and urinary urgency.

Since most falls occur in or around the home, a **home safety evaluation** by a visiting nurse, physical therapist, or health care provider may be beneficial in identifying environmental obstacles and is generally reimbursed by third-party payers, including Medicare.

Table 4–1. Evaluation of gait abnormalities.

Gait Abnormality	Possible Causes
Inability to stand without use of hands	Deconditioning Myopathy (hyperthyroidism, alcohol, statin-induced) Hip or knee pain
Unsteadiness upon standing	Orthostatic hypotension Balance problem (peripheral neuropathy, vision problem, vestibular, other CNS causes) Generalized weakness
Stagger with eyes closed	Often indicates that vision is compensating for another deficit
Short steps	Weakness Parkinson disease or related condition
Asymmetry	Cerebrovascular accident Focal pain or arthritis
Wide-based gait	Fear, balance problems
Flexed knees	Contractures, quadriceps weakness
Slow gait	Fear of falling, weakness, deconditioning, peripheral vascular disease, COPD, heart failure, angina pectoris

Table 4–2. Fall risk factors, targeted interventions, and best evidence for fall prevention.

To Consider for All Patients	
Exercise or physical therapy	Tai Chi, gait training, balance training, strength training
Multifactorial intervention	Home safety assessment, medication review, review of specific conditions (below), advice on appropriate footwear, vision check, adaptive aids as appropriate, physical therapy or exercise as appropriate
Condition	**Targeted Intervention**
Postural hypotension (> 20 mm Hg drop in systolic blood pressure, or systolic blood pressure < 90 mm Hg)	Behavioral recommendations, such as hand clenching, elevation of head of bed; discontinuation or substitution of high-risk medications
Use of benzodiazepine or sedative/hypnotic agent	Education about sleep hygiene; discontinuation or substitution of medications
Use of multiple prescription medications	Review of medications with a focus on discontinuation (deprescribing)
Environmental hazards	Removal or mitigation of hazards; installation of safety equipment (eg, grab bars)
Gait impairment	Gait training, assistive devices, balance or strengthening exercises
Impairment in transfer or balance	Balance exercises, training in transfers, environmental alterations (eg, grab bars)
Impairment in leg or arm muscle strength or limb range of motion	Exercise with resistance bands or putty, with graduated increases in resistance
Vision impairment	Cataract surgery or other interventions as appropriate (eg, corrective lenses)
Inability to get up after a fall	Medical alert system, physical therapy training for fall-prevention strategies
High-risk footwear	Education on appropriate footwear (eg, avoid slippers, high heels)
Osteoporosis	Bisphosphonate treatment to prevent first or recurrent fractures

Complications of Falls

The most common fall-related fractures are of the wrist, hip, and vertebrae. Osteoporosis significantly increases fracture risk, and unfortunately is vastly undertreated in older adults. Following hip fracture, elderly women experience a high mortality rate (approximately 20% in 1 year), particularly if they were debilitated prior to the time of the fracture. Fear of falling again is a common, serious, but treatable factor in the older person's loss of confidence and independence. Referral to a physical therapist for gait training with special devices is often all that is required.

Chronic subdural hematoma is an easily overlooked complication of falls that must be considered in any elderly patient presenting with new neurologic symptoms or signs, including evidence of new cognitive impairment. Headache and known history of trauma may both be absent.

Patients who are unable to get up from a fall are at risk for dehydration, electrolyte imbalance, pressure injuries, rhabdomyolysis, and hypothermia.

Prevention & Management

Exercise is the intervention that is most consistently reported to reduce the risk of falls. Balance focused exercises (eg, Tai Chi), gait, and strength training appear to be more effective for fall prevention than general exercise programs (Table 4–2).

Multifactorial interventions appear to have a small benefit in preventing falls. These interventions include an assessment of potentially modifiable risk factors and tailored interventions to reduce risk. Emphasis is placed on treating all contributory medical conditions, minimizing environmental hazards, and eliminating medications where the harms may outweigh the benefits (eg, sedative-hypnotics).

The USPSTF recommends *against* vitamin D supplementation to prevent falls in community-dwelling adults. Vitamin D supplementation might be considered for high-risk individuals (eg, institutionalized elders) on a case-by-case basis. High-dose vitamin D (60,000 IU per month) has been shown to *increase* the incidence of falls.

Osteoporosis treatment (both preventive and post-fracture) is essential to prevent first and recurrent fracture. First-line treatment with bisphosphonates is very effective; for example, alendronate significantly reduces the risk of hip, vertebral and nonvertebral fracture in people with osteoporosis. Unfortunately, less than 20% of people who sustain a fragility fracture receive osteoporosis treatment (this treatment failure is called the "osteoporosis care gap"; see Chapter 26 for more information).

Assistive devices, such as canes and walkers, are useful for many older adults but often are used incorrectly. Canes should be used on the "good" side. The height of walkers and canes should generally be at about the level of the wrist. Physical therapists are invaluable in assessing the need for an assistive device, selecting the best device, and training a patient in its correct use.

Eyeglasses, particularly bifocal or graduated lenses, may increase the risk of falls, particularly in the early weeks of use. Patients should be counseled about the need to take extra care when new eyeglasses are being used.

Patients with repeated falls are often reassured by the availability of telephones at floor level, a mobile telephone on their person, or a lightweight radio call system. Physical

therapy should also include training in techniques for arising after a fall.

When to Refer

Patients with a recent history of falls should be referred for physical therapy, eye examination, and home safety evaluation.

When to Admit

Consider hospitalization for patients with new falls that are unexplained, particularly in combination with a change in the physical examination (eg, neurologic status) or with an injury/fracture requiring surgery.

Dautzenberg L et al. Interventions for preventing falls and fall-related fractures in community-dwelling older adults: a systematic review and network meta-analysis. J Am Geriatr Soc. 2021;69:2973. [PMID: 34318929]
Ganz DA et al. Prevention of falls in community-dwelling older adults. N Engl J Med. 2020;382:734. [PMID: 32074420]
Liu-Ambrose T et al. Effect of a home-based exercise program on subsequent falls among community-dwelling high-risk older adults after a fall: a randomized clinical trial. JAMA. 2019;321:2092. [PMID: 31162569]
Pahor M. Falls in older adults: prevention, mortality, and costs. JAMA. 2019;321:2080. [PMID: 31162553]
Silverstein WK et al. Closing the osteoporosis care gap: a teachable moment. JAMA Intern Med. 2021;181:1635. [PMID: 34661618]

6. Urinary Incontinence

ESSENTIALS OF DIAGNOSIS

- Involuntary loss of urine.
- *Stress* incontinence: leakage of urine upon coughing, sneezing, or standing.
- *Urge* incontinence: urgency and inability to delay urination.
- *Overflow* incontinence: variable presentation.

General Considerations

Urinary incontinence in older adults is common, and interventions can improve patients' quality of life. Many patients do not voluntarily disclose their experiences with urinary incontinence to their health care providers, possibly due to embarrassment or the belief that it is a normal part of aging. A simple question about involuntary leakage of urine is a reasonable annual screen: "Do you have a problem with urine leaks or accidents?"

Classification

A. Transient Causes

Use of the mnemonic "DIAPPERS" may be helpful in remembering the categories of "transient" urinary incontinence.

1. Delirium—A clouded sensorium impedes recognition of both the need to void and the location of the nearest toilet. Delirium is the most common cause of incontinence in hospitalized patients.

2. Infection—Symptomatic UTI can cause or contribute to urgency and incontinence. Asymptomatic bacteriuria does not.

3. Atrophic urethritis and vaginitis—Atrophic urethritis and vaginitis can usually be diagnosed presumptively by the presence of vaginal mucosal telangiectasia, petechiae, erosions, erythema, or friability. Urethral inflammation, if symptomatic, may contribute to incontinence in some women.

4. Pharmaceuticals—Medications are one of the most common causes of transient incontinence. Typical offending agents include potent diuretics, anticholinergics, psychotropics, opioid analgesics, alpha-blockers (in women), alpha-agonists (in men), and calcium channel blockers.

5. Psychological factors—Severe depression with psychomotor retardation may impede the ability or motivation to reach a toilet.

6. Excess urinary output—Excess urinary output may overwhelm the ability of an older person to reach a toilet in time. In addition to diuretics, common causes include excess fluid intake; metabolic abnormalities (eg, hyperglycemia, hypercalcemia, diabetes insipidus); and peripheral edema (when previously dependent legs assume a horizontal position in bed).

7. Restricted mobility—(See Immobility, above.) If mobility cannot be improved, access to a urinal or commode (eg, at the bedside) may improve continence.

8. Stool impaction—This is a common cause of urinary incontinence in hospitalized or immobile patients. Although the mechanism is still unknown, a clinical clue to its presence is the onset of both urinary and fecal incontinence.

B. Established Causes

Causes of "established" incontinence should be addressed after any "transient" causes have been managed appropriately.

1. Detrusor overactivity (urge incontinence)—Detrusor overactivity refers to uninhibited bladder contractions that cause leakage. It is the most common cause of established incontinence in older adults, accounting for two-thirds of cases. Women will complain of leakage associated with a strong and sudden urge to urinate that cannot be forestalled. In men, the symptoms are similar, but detrusor overactivity commonly coexists with urethral obstruction from benign prostatic hyperplasia. Because detrusor overactivity also may be due to bladder stones or tumor, the abrupt onset of otherwise unexplained urge incontinence—especially if accompanied by perineal or suprapubic discomfort or sterile hematuria—should be investigated by urine cytology and cystoscopy.

2. Urethral incompetence (stress incontinence)— Urethral incompetence is the second most common cause of established urinary incontinence in older women. In men, it commonly occurs after radical prostatectomy. Stress incontinence is characterized by instantaneous leakage of urine in response to an increase in intra-abdominal pressure. It can coexist with detrusor overactivity causing "mixed" incontinence. Typically, urinary loss occurs with laughing, coughing, or lifting heavy objects. To test for stress incontinence, have the patient relax the perineum and cough vigorously (a single cough) while standing with a full bladder. Instantaneous leakage indicates stress incontinence. A delay of several seconds or persistent leakage suggests that the problem is instead caused by an uninhibited bladder contraction induced by coughing.

3. Overflow incontinence—Urethral obstruction (due to prostatic enlargement, urethral stricture, bladder neck contracture, or prostatic cancer) is a common cause of established incontinence in older men but is rare in older women. It can present as dribbling incontinence after voiding, urge incontinence due to detrusor overactivity, or overflow incontinence due to urinary retention. Detrusor underactivity is less common but can also cause overflow incontinence. It may be idiopathic or have an identifiable cause including medications and sacral lower motor nerve dysfunction. When it causes incontinence, detrusor underactivity is associated with urinary frequency, nocturia, and frequent leakage of small volumes.

Treatment

A. Transient Causes

Each identified transient cause should be treated regardless of whether an established cause coexists. For patients with urinary retention induced by an anticholinergic agent, discontinuation of the medication should first be considered. If this is not feasible, substituting a less anticholinergic agent may be useful.

B. Established Causes

1. Detrusor overactivity—The cornerstone of treatment is **bladder training.** Patients start by voiding on a schedule based on the shortest interval recorded on a bladder record. They then gradually lengthen the interval between voids by 30 minutes each week using relaxation techniques to postpone the urge to void. Lifestyle modifications, including weight loss and caffeine reduction, may also improve incontinence symptoms. For cognitively impaired patients and nursing home residents who are unable to manage on their own, **timed and prompted voiding** initiated by caregivers is effective. **Pelvic floor muscle ("Kegel") exercises** can reduce the frequency of incontinence episodes when performed correctly and sustained.

If behavioral approaches prove insufficient, several FDA-approved **antimuscarinic agents** may provide additional benefit. Available regimens of these agents include short-acting tolterodine, 1–2 mg orally twice a day; long-acting tolterodine, 2–4 mg orally daily; short-acting oxybutynin, 2.5–5 mg orally twice or three times a day; long-acting oxybutynin, 5–15 mg orally daily; oxybutynin transdermal patch, 3.9 mg/day applied twice weekly; oxybutynin 10% transdermal gel, 100 mg applied daily; fesoterodine, 4–8 mg orally once daily; trospium chloride, 20 mg orally once or twice daily; long-acting trospium chloride, 60 mg orally daily; darifenacin, 7.5–15 mg orally daily; and solifenacin, 5–10 mg orally daily. All of these agents appear to have similar efficacy and side-effect profiles (eg, delirium/cognitive impairment, dry mouth, constipation, urinary retention). Long-acting and topical preparations are generally better tolerated.

The beta-3-agonists **mirabegron,** 25–50 mg orally daily, and vibegron, 75 mg orally once daily, are FDA approved for overactive bladder symptoms, which include urge urinary incontinence. In trials comparing mirabegron with antimuscarinic agents, the efficacy and safety profiles have been comparable, with less dry mouth reported in persons who received mirabegron. The experience accruing among adults over the age of 70 shows that adherence rates may be superior to the antimuscarinic medications.

An alternative to oral agents is an injection of **onabotulinum toxin A** into the detrusor muscle. While effective, it can lead to urinary retention and the need for self-catheterization.

The combination of behavioral therapy and antimuscarinics appears to be more effective than either alone, although one study in a group of younger women showed that adding behavioral therapy to individually titrated doses of extended-release oxybutynin was no better than with medication treatment alone.

In men with both benign prostatic hyperplasia and detrusor overactivity and with postvoid residual of 150 mL or less, an antimuscarinic agent added to an alpha-blocker may provide additional relief of lower urinary tract symptoms.

2. Urethral incompetence (stress incontinence)— **Lifestyle modifications,** including limiting caffeine and fluid intake, may be helpful for some women, particularly women with mixed stress/urge incontinence; strong evidence supports weight loss in obese women. **Pelvic floor muscle exercises** are effective for women with mild to moderate stress incontinence. Instruct the patient to pull in the pelvic floor muscles and hold for 6–10 seconds and to perform three sets of 8–12 contractions daily. Benefits may not be seen for 6 weeks. **Pessaries** or **vaginal cones** may be helpful in some women but should be prescribed only by providers who are experienced with using these modalities.

No medications are approved for the treatment of stress incontinence, and a clinical practice guideline from the American College of Physicians recommends against pharmacologic treatment. Although a last resort, **surgery** is the most effective treatment for stress incontinence; cure rates as high as 96% can result, even in older women.

3. Overflow incontinence—Most men with overflow incontinence from obstructive uropathy will first undergo bladder decompression with intermittent or indwelling catheterization followed by initiation of alpha-blocking agents (eg, terazosin, 1–10 mg orally daily; prazosin, 1–5 mg orally twice daily; or tamsulosin, 0.4–0.8 mg orally

daily taken 30 minutes after a meal). Finasteride, 5 mg orally daily, can provide additional benefit in men with an enlarged prostate. If medical therapy fails to allow for adequate bladder emptying, surgical decompression can be an option. A variety of nonsurgical techniques make decompression feasible even for frail men. For the nonoperative candidate with urinary retention, intermittent or indwelling catheterization is used. For the patient with a poorly contractile bladder, augmented voiding techniques (eg, double voiding, suprapubic pressure) can prove effective. If further emptying is needed, intermittent or indwelling catheterization is the only option. Antibiotics should be used only for symptomatic UTI or as prophylaxis against recurrent symptomatic infections in a patient using intermittent catheterization; they should not be used as prophylaxis in a patient with an indwelling catheter.

When to Refer

- Men with urinary obstruction who do not respond to medical therapy should be referred to a urologist.
- Women who do not respond to medical and behavioral therapy should be referred to a urogynecologist or urologist.

Sung VW et al. Effect of behavioral and pelvic floor muscle therapy combined with surgery vs surgery alone on incontinence symptoms among women with mixed urinary incontinence: the ESTEEM randomized clinical trial. JAMA. 2019;322:1066. [PMID: 31529007]

Vaughan CP et al. Urinary incontinence in women. Ann Intern Med. 2020;172:ITC17. [PMID: 32016335]

7. Involuntary Weight Loss

General Considerations

Aging, even in the absence of disease, is associated with reduced appetite. Involuntary weight loss affects substantial numbers of older adults. Most studies of involuntary weight loss in community-dwelling older adults define it as loss of 5% of body weight in 6 months or 10% of body weight in 1 year.

Clinical Findings

The many potential causes of involuntary weight loss include **medical conditions** (60–70%; eg, cancer cachexia, chronic heart failure) and **psychiatric conditions** (10–20%; eg, depression), but in up to 25%, the cause of weight loss cannot be identified. **Social factors,** such as access to food and dental health, should be investigated. The clinical evaluation should search for symptoms and signs that could point to a potential cause (eg, abdominal pain to peptic ulcer disease; tachycardia to hyperthyroidism). When the history, physical examination, and basic laboratory studies do not suggest a possible diagnosis, additional evaluation (eg, total body CT scan) is usually low yield. When no other cause is identified, the frailty syndrome should be considered in the differential diagnosis.

Treatment

Initial treatment should focus on identifying medical causes of involuntary weight loss while also addressing and improving social barriers, such as social isolation and access to food. Social meals can improve intake and nutrition. Oral nutritional supplements of 200–1000 kcal/day can increase weight and improve outcomes in malnourished hospitalized older adults but have *not* been shown to have benefits in community-dwelling older adults. Sodium-containing flavor enhancers (eg, iodized salt) can improve food intake without adverse health effects when there is no contraindication to their use. Megestrol acetate as an appetite stimulant has *not* been shown to increase lean body mass or lengthen life among elders and has significant side effects. For those patients with advanced dementia, percutaneous liquid artificial nutrition ("tube feeding") is *not* recommended, but rather assiduous hand feeding may allow maintenance of weight and provide more comfort.

8. Pressure Injury

ESSENTIALS OF DIAGNOSIS

- Examine at-risk patients on admission to the hospital and daily thereafter.
- Pressure injury is classified into one of six categories:
  - Stage 1: Non-blanchable erythema of intact skin
  - Stage 2: Partial-thickness skin loss with exposed dermis
  - Stage 3: Full-thickness skin loss
  - Stage 4: Full-thickness skin and tissue loss
  - Unstageable: Obscured full-thickness skin and tissue loss
  - Deep tissue: Persistent non-blanchable, deep red, maroon, or purple discoloration

General Considerations

The National Pressure Injury Advisory Panel changed the term "pressure ulcer" to "pressure injury" to more accurately reflect the fact that stage 1 and deep tissue injury describe damage to intact skin, compared to the ulcers described in the other four stages. Deep tissue and unstageable pressure injury are included in the six pressure injury stages. An area of purple or maroon discolored intact skin or blood-filled blister is characteristic of deep tissue injury, sometimes preceded by tissue that is painful, firm, mushy, boggy, warmer, or cooler compared with adjacent tissue. Ulcers in which the base is covered by slough (yellow, tan, gray, green, or brown) or eschar (tan, brown, or black) are considered unstageable. Most pressure injuries develop during an acute illness. The primary risk factor for pressure injuries is immobility. Other contributing risk factors include reduced sensory perception, moisture (urinary and

fecal incontinence), poor nutritional status, and friction and shear forces.

Older adults admitted to hospitals and nursing homes should be assessed for their risk of developing pressure injuries, and several risk assessment instruments can be used, including the Braden Scale and the Norton score. These tools should be used in conjunction with clinical judgment since each may cover a limited range of risk factors and each depends on the skills of examiner.

Prevention

Using specialized support surfaces (including mattresses, beds, and cushions), patient repositioning, optimizing nutritional status, reducing shear and friction forces, and moisturizing sacral skin are strategies that have been shown to reduce pressure injury. In general, advanced supportive surfaces are superior to standard hospital beds in preventing and managing pressure injuries, but there is no clear advantage of one support surface over another.

Evaluation

Evaluation of pressure injuries should include patient's risk factors and goals of care; injury stage, size, and depth; absence or presence (and type) of exudate; appearance of the wound bed and possible surrounding infection; and sinus tracking, or cellulitis.

Treatment

High-quality evidence that rigorously examines the effectiveness of various treatments remains limited. Clinicians should therefore focus on the principles of wound care, including pressure reduction, removing necrotic debris, and maintaining a moist wound bed that will promote healing and formation of granulation tissue. The type of dressing that is recommended depends on the location and depth of the wound, whether necrotic tissue or dead space is present, and the amount of exudate (Table 4–3). Pressure-reducing devices (eg, air-fluid beds and low-air-loss beds) are associated with improved healing rates. Although poor nutritional status is a risk factor for the development of pressure injury, the evidence that nutritional supplementation helps correct pressure injury is limited.

Providers can become easily overwhelmed by the array of products available for the treatment of established pressure injuries. Most institutions should designate a wound care expert or team to select a streamlined wound care product line that has simple guidelines. In a patient with end-stage disease who is receiving end-of-life care, appropriate treatment might be directed toward palliation only (including minimizing dressing changes and odors) rather than efforts directed at healing.

Table 4–3. Pressure injury dressings and other measures.

Injury Type	Dressing Type and Considerations
Stage 1	Polyurethane film Hydrocolloid wafer
Stage 2	Hydrocolloid wafers Semipermeable foam dressing Polyurethane film
Stages 3 and 4	For highly exudative wounds, use highly absorptive dressing or packing, such as calcium alginate Wounds with necrotic debris must be debrided Debridement can be autolytic, enzymatic, or surgical Shallow, clean wounds can be dressed with hydrocolloid wafers, semipermeable foam, or polyurethane film Deep wounds can be packed with gauze; if the wound is deep and highly exudative, an absorptive packing should be used
Heel injury	Do not remove eschar on heel pressure injury because it can help promote healing (eschar in other locations should be debrided)
Unstageable	Debride if appropriate before deciding on further therapy
Deep tissue injury	Offload pressure to the affected area

Complications

Bacteria contaminate all chronic pressure injuries with skin loss, but it can be difficult to identify those wounds that are infected. Suspicion for infection should rise if there is pain, increased or foul-smelling wound drainage, erythema of the skin around the wound, or if the wound will not heal. Fever and leukocytosis are other indicators of systemic infection but are not always present. Culture from a superficial swab adds little valuable diagnostic information. For nonhealing infected wounds without evidence of systemic involvement, topical antiseptics (eg, silver sulfadiazine) are recommended and may need to be accompanied by debridement of necrotic tissue. When systemic infections such as cellulitis and osteomyelitis are present, oral or parenteral antibiotics are warranted and medication choice should be guided by tissue culture, but obtaining this can be painful and it is not always readily available.

When to Refer

- Pressure injuries that are large or nonhealing should be referred to a plastic or general surgeon or dermatologist for biopsy, debridement, and possible skin grafting.
- For hospitalized patients or residents of skilled nursing facilities in whom pressure injuries develop, early involvement of a wound care specialist is crucial.

When to Admit

Patients with pressure injury should be admitted if the primary residence is unable to provide adequate wound care or pressure reduction, or if the wound is infected or requires complex or surgical care.

Gillespie BM et al. Repositioning for pressure injury prevention in adults. Cochrane Database Syst Rev. 2020;6:CD009958. [PMID: 32484259]
Hajhosseini B et al. Pressure injury. Ann Surg. 2020;271:671. [PMID: 31460882]
Moore Z et al. Prevention of pressure ulcers among individuals cared for in the prone position: lessons for the COVID-19 emergency. J Wound Care. 2020;29:312. [PMID: 32530776]

9. Pharmacotherapy & Polypharmacy

ESSENTIALS OF DIAGNOSIS

- Older adults experience more adverse drug events than younger patients. Evaluate for dose reduction or drug avoidance based on kidney function, comorbidities, and other medication use.
- The AGS Beers Criteria list is useful for identifying high-risk medications for older adults. Particular caution/avoidance should be used in prescribing benzodiazepines and other sedative-hypnotic medications.

General Considerations

Definitions of polypharmacy vary; it typically refers to the condition of taking or being prescribed a multitude of prescription and nonprescription medications. More adverse drug events occur in older adults compared to younger patients for many reasons, including changing drug metabolism in the kidney or liver or both, drug interaction with comorbid conditions, and interactions between multiple medications. Polypharmacy itself is associated with adverse health outcomes, including falls, impaired cognition, hospitalizations, and death.

Medication metabolism is often impaired in older adults due to decreased GFR, reduced hepatic clearance, and changes in body composition (eg, lean body mass). Most emergency hospitalizations for adverse medication events among older adults result from commonly prescribed medications used alone or in combination.

Precautions in Prescribing Medications

Most medications prescribed for chronic disease management should be initiated at the low end of the usual adult dosage range, with slow increases in dosage until a therapeutic level is reached or intolerable side effects develop. At the same time, it is imperative that a medication's therapeutic dose be achieved, since older adults are at risk for undertreatment of conditions such as depression, if the starting dose is not increased with careful monitoring.

Optimal medication adherence is less likely with increasing numbers of pills and doses, high cost, poor communication about medication changes as well as expected benefits and side effects; other factors affecting adherence include cognitive impairment, insurance issues, and psychosocial barriers. When possible, the clinician should simplify both dosing schedules with the fewest number of pills and doses (combination formulations can be useful in this regard, though perhaps complicating future dose adjustments) as well as modes of administration (eg, oral, ocular, transdermal, subcutaneous, inhalational). Other helpful medication management techniques include use of a single pharmacy, use of pillboxes or pharmacy-packaged medication sets, clarity about the prescriber of each medication (and ideally use of fewer prescribers), infrequent medication changes, and clear instructions about all medication changes using the "teach-back" method of patient communication. Clinicians should ask patients about their ability to afford their medications, and counsel patients about strategies for cost containment (eg, switching to a more affordable Medicare Part D plan during open enrollment and interrogating drug formularies for low-cost alternatives).

The patient or caregiver should bring in all medications at each visit in order to achieve an accurate **medication reconciliation** and reinforce reasons for medication use, dosage, frequency of administration, and possible adverse effects. Patients should also bring all supplements and over-the-counter medications used, including analgesics and sleep aids. Medication reconciliation is particularly important if the patient sees multiple clinicians. Clinicians should be aware of the "prescribing cascade" in which a medication is prescribed to counter the side effect of another medication.

The risk of toxicity goes up with the number of medications prescribed. Certain combinations of medications (eg, warfarin and many antibiotics, ACE inhibitors and NSAIDs, opioids and sedative-hypnotics) are particularly likely to cause drug-drug interactions and should be monitored carefully.

Trials of medication discontinuation (deprescribing) should be considered when the original indication is unclear or the patient is having side effects. Medication discontinuation is particularly important in patients with limited life expectancy who may be experiencing increasing burdens from polypharmacy and modest, if any, benefits from the medication (eg, bisphosphonates, antilipemics). Clinical tools such as "STOPP/START" and the AGS Beers Criteria can inform safe medication prescribing for older adults.

When to Refer

- Refer patients with polypharmacy or poor medication adherence to a clinical pharmacist, when available.
- Refer homebound patients with poor medication adherence and suboptimal chronic disease management to a home health nurse for medication reconciliation and teaching.

Fick DM et al. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67:674. [PMID: 30693946]
Hoel RW et al. Polypharmacy management in older patients. Mayo Clin Proc. 2021;96:242. [PMID: 33413822]
Nicosia FM et al. What is a medication-related problem? A qualitative study of older adults and primary care clinicians. J Gen Intern Med. 2020;35:724. [PMID: 31677102]

Thevelin S et al. Potentially inappropriate prescribing and related hospital admissions in geriatric patients: a comparative analysis between the STOPP and START criteria versions 1 and 2. Drugs Aging. 2019;36:453. [PMID: 30694444]

10. Vision Impairment

Visual impairment due to age-related refractive error ("presbyopia"), macular degeneration, cataracts, glaucoma, or diabetic retinopathy is associated with several negative physical and mental health outcomes. These include falls, impaired mobility, and reduced quality of life. While the 2016 USPSTF guideline and 2018 Cochrane Review conclude that there is insufficient evidence for routine visual impairment screening, the American Academy of Ophthalmology recommends a complete eye examination every 1–2 years after age 65. Serious and correctable vision disorders are prevalent and morbid enough that it is reasonable for most elders to undergo a comprehensive eye examination by an ophthalmologist or optometrist every 1–2 years. Eye examinations should certainly be prioritized for patients with new or recurring falls, changes in vision, and conditions with risk of eye complications (eg, diabetes mellitus, thyroid disease). Patients with significant visual loss should be referred to low-vision community programs for support and assessment for assistive devices.

Assi L et al. A global assessment of eye health and quality of life: a systematic review of systematic reviews. JAMA Ophthalmol. 2021;139:526. [PMID: 33576772]
Ehrlich JR et al. Prevalence of falls and fall-related outcomes in older adults with self-reported vision impairment. J Am Geriatr Soc. 2019;67:239. [PMID: 30421796]

11. Hearing Impairment

Hearing loss in older adults is very common yet often undertreated. Over one-third of persons older than age 65 and half of those older than age 85 have some degree of hearing loss. Hearing loss is associated with social isolation, depression, disability, cognitive impairment and accelerated cognitive decline, hospitalization, and nursing home placement. Hearing loss is undertreated because it is underrecognized by clinicians and hearing assistive devices are expensive and not typically covered by insurance.

Although the USPSTF found insufficient evidence for routine hearing screening, clinicians should periodically ask patients about hearing loss and refer them to audiology if hearing loss is suspected. A reasonable clinical screen is to ask patients if they have noticed any hearing impairment. Those who answer "yes" should be referred for audiometry. For those who answer "no" but in whom hearing loss is still suspected, further in-office screening can be performed using the **whispered voice test.** To determine the degree to which hearing impairment interferes with functioning, the provider may ask patients if they become frustrated when conversing with family members, have challenges understanding conversations, are embarrassed when meeting new people, or have difficulty watching television. Caregivers or family members can provide important collateral information regarding potential hearing loss and the impact of hearing loss on social interactions.

Hearing loss assistive devices and technology include hearing aids, cochlear implants, sound amplification for telephones and televisions, speech to text software, smart phone applications, hearing loops, and alerting devices to inform hearing-impaired people of an event such as a fire alarm. Hearing amplification and cochlear implantation improve hearing-related quality of life and reduce depressive symptoms. Compliance with hearing amplification can be a challenge because of the high device cost, dissatisfaction with performance, and stigma associated with hearing aid use. Newer digital devices may perform better but are considerably more expensive. US federal law allows for the sale of over-the-counter devices that can be purchased directly without a prescription from a clinician. These devices are most appropriate for patients with mild to moderate hearing loss. Cochlear implantation is an underutilized treatment that is recommended for older adults with profound sensory hearing loss. It improves understanding of speech and quality of life. Portable hearing amplifiers (eg, "pocket talkers") are low-cost hand-held devices with a headset for the patient and microphone to amplify sound for the speaker. These devices are particularly useful to communicate with hearing-impaired patients in clinic and inpatient settings. In order to facilitate successful communication with hearing-impaired patients, providers should face toward patients when speaking, speak at a moderate pace and in a low tone, and practice the "teachback" method in order to assess that information was adequately transmitted.

Alattar AA et al. Hearing impairment and cognitive decline in older, community-dwelling adults. J Gerontol: Series A. 2020; 75:567. [PMID: 30753308]
Carlson ML. Cochlear implantation in adults. N Engl J Med. 2020;382:1531. [PMID: 32294347]
Feltner C et al. Screening for hearing loss in older adults: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2021;325:1202. [PMID: 33755082]
US Preventive Services Task Force; Krist AH et al. Screening for hearing loss in older adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2021;325:1196. [PMID: 33755083]

12. Elder Mistreatment & Self-Neglect

Elder abuse is defined as "acts whereby a trusted person causes or creates risk of harm to an older adult." **Self-neglect** is the most common form of elder abuse and occurs among all demographic strata. In the United States, about 10% of adults over age 60 have experienced some sort of abuse or neglect in the previous year. Financial abuse is on the rise, and older adults with cognitive impairment are particularly vulnerable. Each year, at least 5% of elders are victims of financial abuse or scams.

Elder abuse risk factors include limited social support and poor physical health. Clues to the presence of elder mistreatment or self-neglect include observing that the patient's behavior changes in the presence of the caregiver, delays between injury occurrence and treatment seeking,

Table 4–4. Phrases and actions that may be helpful in situations of suspected abuse or neglect.

Questions for the Elder
1. Has anyone hurt you?
2. Are you afraid of anybody?
3. Is anyone taking or using your money without your permission?
Questions for the Caregiver
1. Are your relative's needs more than you can handle?
2. Are you worried that you might hit your relative?
3. Have you hit your relative?
If abuse is suspected
Tell the patient that you are concerned, want to help, and will call Adult Protective Services for further assistance
Document any injuries
Document the patient's words
Document whether the patient has decision-making capacity using a tool such as "Aid to Capacity Evaluation"

inconsistencies between an observed injury and its associated explanation, lack of appropriate clothing or hygiene, and unfilled prescriptions. Elder abuse and self-neglect can cause many health consequences, such as long-term care placement, anxiety, depression, and death.

While the USPSTF has not endorsed any screening tools to identify elder abuse, clinicians caring for older adults should maintain a high index of suspicion and meet with patients without the presence of caregivers on occasion. Vigilance for possible elder abuse is important across care settings including residential care facilities, ambulatory settings, and emergency departments. In these encounters, clinicians can ask questions about the caregiver relationship, and directly question about possible mistreatment and neglect, if suspected (Table 4–4).

When self-neglect is suspected, it is critical to establish whether a patient has decision-making capacity regarding the suspected neglectful behavior. A patient who has full decision-making capacity should be provided help and support but can choose to live in conditions of self-neglect, providing that the public is not endangered by their actions. In contrast, more aggressive intervention is recommended for a patient who lacks decision-making capacity and lives in conditions of self-neglect. Such interventions include reporting to Adult Protective Services and arranging in-home help, conservatorship, and placement in a supervised setting. Cognitive assessment may provide some insight into whether cognitive impairment is contributing to self-neglect, but these tools are not designed to assess decision-making capacity. A standardized tool, such as the "Aid to Capacity Evaluation," is easy to administer, has good performance characteristics for determining decision-making capacity, and is available free online at https://www.jcb.utoronto.ca/tools/documents/ace.pdf.

When to Refer

- Refer older adults suffering from suspected elder abuse or self-neglect to **Adult Protective Services**, as required by law in most states (consult the National Center on Elder Abuse at https://ncea.acl.gov/)
- Refer to a mental health professional and neurologist for evaluation of those cases in which decision-making capacity is unclear, neuropsychiatric testing would be useful, or if untreated mental illness is suspected to play a role in self-neglect.

When to Admit

- Admit older adults who would be unsafe in the community when an alternative plan cannot be put into place in a timely manner. In cases of self-neglect, surrogate decision-makers need to be identified and conservatorship may need to be pursued for safe discharge planning.

Cimino-Fiallos N et al. Elder abuse—a guide to diagnosis and management in the emergency department. Emerg Med Clin North Am. 2021;39:405. [PMID: 33863468]

DeLiema M et al. Financial fraud among older Americans: evidence and implications. J Gerontol B Psychol Sci Soc Sci. 2020;75:861. [PMID: 30561718]

Van Den Bruele AB et al. Elder abuse. Clin Geriatr Med. 2019;35:103. [PMID: 30390976]

Palliative Care & Pain Management

5

Michael W. Rabow, MD
Steven Z. Pantilat, MD
Ann Cai Shah, MD
Lawrence Poree, MD, MPH, PhD
Raj Mitra, MD

PALLIATIVE CARE

DEFINITION & SCOPE

Palliative care is medical care focused on improving quality of life for people living with serious illness. Serious illness is defined as "a condition that carries a high risk of mortality, negatively impacts quality of life and daily function, and/or is burdensome in symptoms, treatments or caregiver stress." Palliative care addresses and treats symptoms, supports patients' families and loved ones, and through clear communication helps ensure that care aligns with patients' preferences, values, and goals. Near the end of life, palliative care may become the sole focus of care, but palliative care *alongside* cure-focused treatment or disease management is beneficial throughout the course of a serious illness, regardless of its prognosis. Randomized studies have shown that palliative care provided alongside disease-focused treatment can improve quality of life, promote symptom management, and even prolong life in some situations.

Palliative care includes management of physical symptoms, such as pain, dyspnea, nausea and vomiting, constipation, delirium, and agitation; emotional distress, such as depression, anxiety, and interpersonal strain; and existential distress, such as spiritual crisis. While palliative care is a medical subspecialty recognized by the American Board of Medical Specialties ("specialty palliative care") and is typically provided by an interdisciplinary team of experts, *all* clinicians should have the skills to provide "primary palliative care" including managing pain; treating dyspnea; addressing mood disorders; communicating about prognosis and patient preferences for care; and helping address spiritual distress. The fourth edition of the National Consensus Project's Clinical Practice Guidelines for Quality Palliative Care emphasizes that palliative care is the responsibility of all clinicians and disciplines caring for people with serious illness in all health care settings, including hospitals, primary care and specialty clinics, nursing homes, and the community. The scope of primary palliative care and the ideal timing to begin specialty palliative care for patients with different illnesses is an evolving area of practice.

As is true for clinicians of all medical specialties, palliative care clinicians and the systems of care for people with serious illness in the United States are influenced by systemic racial bias. Knowing that there are racial inequities in palliative care referral, pain management, communication, and outcomes, practitioners must work to identify and rectify injustice in how patient symptoms are assessed and treated and ensure equal access to palliative care services.

Fadul N et al. Integration of palliative care into COVID-19 pandemic planning. BMJ Support Palliat Care. 2021;11:40. [PMID: 32527790]
Kluger BM et al. Comparison of integrated outpatient palliative care with standard care in patients with Parkinson disease and related disorders: a randomized clinical trial. JAMA Neurol. 2020;77:551. [PMID: 32040141]
Mechler K et al. Palliative care approach to chronic diseases: end stages of heart failure, chronic obstructive pulmonary disease, liver failure, and renal failure. Prim Care. 2019;46:415. [PMID: 31375190]
Ornstein KA et al. Evaluation of racial disparities in hospice use and end-of-life treatment intensity in the REGARDS cohort. JAMA Netw Open. 2020;3:e2014639. [PMID: 32833020]

PALLIATION OF COMMON NONPAIN SYMPTOMS

GENERAL PRINCIPLES

During any stage of illness, patients should be screened routinely for symptoms. Any symptoms that cause significant suffering should be addressed quickly and aggressively with frequent elicitation, individualized treatment, and reassessment. While patients at the end of life may experience a host of distressing symptoms, pain, dyspnea, and delirium are among the most feared and burdensome.

DYSPNEA

Dyspnea is the subjective experience of difficulty breathing and may be characterized by patients as tightness in the chest, shortness of breath, breathlessness, or a feeling of suffocation. Up to half of people at the end of life may experience severe dyspnea.

Treatment of dyspnea is first directed at the cause (see Chapter 9) if a workup is consistent with the patient's goals. Dyspnea responds to opioids, which have been proven effective in multiple randomized trials. Starting doses are typically lower than would be necessary for the relief of moderate pain. Immediate-release morphine given orally (2–4 mg every 4 hours) or intravenously (1–2 mg every 4 hours) treats dyspnea effectively. Sustained-release morphine given orally at 10 mg daily is safe and effective for most patients with ongoing dyspnea. Many patients who become seriously ill with COVID-19 experience dyspnea and may require opioids as well as supplemental oxygen. Supplemental oxygen may be useful for the dyspneic patient *who is hypoxic* with any illness. Fresh air from a window or fan may provide relief for dyspneic patients who are not hypoxic. Judicious use of noninvasive ventilation (eg, high-flow oxygen via nasal cannula) as well as meditation and guided imagery may benefit some patients. Benzodiazepines may be useful for treatment of dyspnea-related anxiety.

NAUSEA & VOMITING

Nausea and vomiting are common and distressing symptoms. Management of nausea may be optimized by regular dosing and often requires multiple medications targeting one or more of the four major inputs to the vomiting center (see Chapter 15).

Vomiting associated with opioids is discussed below. Some patients with prolonged vomiting will require hospitalization. Nasogastric suction may provide rapid, short-term relief for vomiting associated with constipation (in addition to laxatives), gastroparesis, or gastric outlet or bowel obstruction. Metoclopramide (5–20 mg orally or intravenously four times a day) can be helpful in partial gastric outlet obstruction. Transdermal scopolamine (1.5-mg patch every 3 days) can reduce peristalsis and cramping pain, and H_2-blocking medications can reduce gastric secretions. High-dose corticosteroids (eg, dexamethasone, 20 mg orally or intravenously daily in divided doses) can be used in refractory cases of nausea or vomiting or when it is due to bowel obstruction or increased intracranial pressure. Malignant bowel obstruction in people with advanced cancer is a poor prognostic sign and surgery is rarely helpful.

Benzodiazepines (eg, lorazepam, 0.5–1.0 mg given orally every 6–8 hours) can be effective in preventing the *anticipatory* nausea and anxiety associated with chemotherapy. For emetogenic chemotherapy, treatment includes combinations of 5-HT_3-antagonists (eg, ondansetron, granisetron, or palonosetron), neurokinin-1 receptor antagonists (eg, aprepitant, fosaprepitant, or rolapitant), the N-receptor antagonist netupitant combined with palonosetron (NEPA), olanzapine, dexamethasone, or prochlorperazine. In addition to its effect on mood, mirtazapine, 15–45 mg orally nightly, may improve nausea and appetite. Finally, dronabinol (2.5–20 mg orally every 4–6 hours) can help with nausea and vomiting. Patients report relief from medical cannabis, although it is unclear which tetrahydrocannabinol (THC) or cannabidiol (CBD) strains are most effective.

CONSTIPATION

Given the frequent use of opioids, poor dietary intake, physical inactivity, and lack of privacy, constipation is a common problem in seriously ill and dying patients. Clinicians must inquire about any difficulty with hard or infrequent stools. Constipation is an easily preventable and treatable cause of discomfort, distress, and nausea and vomiting (see Chapter 15).

Constipation may be prevented or relieved if patients can increase their activity and intake of fluids. Provision of privacy, undisturbed toilet time, and a bedside commode rather than a bedpan, may be important for some patients.

A prophylactic bowel regimen with a stimulant laxative (senna or bisacodyl) should be started when opioid treatment is begun. Table 15–4 lists other agents (including **osmotic laxatives such as polyethylene glycol** and lactulose) that can be added as needed. Docusate, a stool softener, is *not* recommended because it does not add benefit beyond stimulant laxatives. Peripherally acting mu-receptor antagonists (including oral naloxegol and naldemedine, and subcutaneous methylnaltrexone) are recommended to treat laxative-refractory opioid-induced constipation. Evidence is insufficient to recommend lubiprostone or prucalopride. Patients who report being constipated and then have diarrhea typically are passing liquid stool around impacted stool. Such patients should have a rectal examination to assess for impaction; if it is present, disimpaction will be required.

FATIGUE

Fatigue is the most common complaint among people with cancer. Anemia, hypothyroidism, hypogonadism, cognitive and functional impairment, and malnutrition can contribute to fatigue and should be corrected if possible (and desired by the patient). Because pain and depression often coexist with fatigue as a "symptom cluster," they should be managed appropriately in fatigue. Fatigue from medication adverse effects and polypharmacy is common and should be addressed. For nonspecific fatigue, physical activity, rehabilitation, and exercise may be effective. Although psychostimulants, such as methylphenidate (5–10 mg orally in the morning and afternoon) or modafinil (100–200 mg orally in the morning), are commonly used for cancer-related fatigue, strong evidence for effectiveness is lacking. American ginseng (*Panax quinquefolius*) has been shown to be effective for cancer-related fatigue but may have an estrogenic effect. Corticosteroids may have a short-term benefit. Venlafaxine and buproprion tend to be activating. Caffeinated beverages can help.

DELIRIUM & AGITATION

Many patients die in a state of delirium—a waxing and waning in level of consciousness and a change in cognition that develops over a short time and is manifested by misinterpretations, illusions, hallucinations, sleep-wake cycle disruptions, psychomotor disturbances (eg, lethargy, restlessness), and mood disturbances (eg, fear, anxiety). Delirium may be hyperactive, hypoactive, or mixed. Agitated

delirium at the end of life is also called **terminal restlessness.**

While some patients with delirium may appear "pleasantly confused," it is difficult to know what patients experience. In the absence of obvious distress in the patient, a decision by the patient's family and clinicians not to treat delirium may be prudent. Agitated delirium at the end of life, however, is often distressing to patient and family and requires treatment. Delirium may interfere with the family's ability to interact with the patient and may prevent a patient from being able to recognize and report important symptoms. Common reversible causes of delirium include urinary retention, constipation, pain, and anticholinergic medications; these should be addressed whenever possible. There is no evidence that dehydration causes or that hydration relieves delirium. Careful attention to patient safety and nonpharmacologic strategies to help the patient remain oriented (clock, calendar, familiar environment, reassurance and redirection from caregivers) may be sufficient to prevent or manage mild delirium. Benzodiazepines can worsen delirium and generally should be avoided, though they may be helpful in achieving sedation near the end of life. A randomized trial of placebo compared to risperidone or haloperidol in delirious patients demonstrated *increased* mortality with neuroleptics. Thus, **neuroleptic agents generally should be avoided.** When agitated delirium is refractory to other treatments and remains intolerable, however, especially at the end of life, neuroleptic agents (eg, haloperidol, 1–10 mg orally, subcutaneously, intramuscularly, or intravenously twice or three times a day, or risperidone, 1–3 mg orally twice a day) or frank sedation with barbiturates or benzodiazepines may be required (eg, midazolam, 0.5–5 mg/h subcutaneously or intravenously).

Davis MP et al. The benefits of olanzapine in palliating symptoms. Curr Treat Options Oncol. 2020;22:5. [PMID: 33244634]
Keeley P et al. Symptom burden and clinical profile of COVID-19 deaths: a rapid systematic review and evidence summary. BMJ Support Palliat Care. 2020;10:381. [PMID: 32467101]
Klasson C et al. Fatigue in cancer patients in palliative care—a review on pharmacological interventions. Cancers (Basel). 2021;13:985. [PMID: 33652866]
Sarrió RG et al; Working Group ActEIO Project. Delphi consensus on strategies in the management of opioid-induced constipation in cancer patients. BMC Palliat Care. 2021;20:1. [PMID: 33388041]
Verberkt CA et al. Effect of sustained-release morphine for refractory breathlessness in chronic obstructive pulmonary disease on health status: a randomized clinical trial. JAMA Intern Med. 2020;180:1306. [PMID: 32804188]

DECISION MAKING FOR PATIENTS WITH SERIOUS ILLNESS

Advance Care Planning & Advance Directives

The idea that patients must choose between quality and quantity of life is an outmoded concept that presents patients with a false choice. Clinicians should discuss with patients that an approach that provides *concurrent* palliative and disease-focused care is the one most likely to achieve improvements in both quality *and* quantity of life. Well-informed, competent adults have a right to refuse life-sustaining interventions, even if this would result in death. In order to promote patient autonomy, clinicians are obligated to inform patients about the risks, benefits, alternatives, and expected outcomes of medical interventions, such as CPR, mechanical ventilation, hospitalization and ICU care, and artificial nutrition and hydration.

Advance directives (**ADs**) are oral or written statements made by patients when they are competent that project their autonomy into the future. ADs are intended to guide care should patients lose the ability to make and communicate their own decisions. ADs are an important part of **advance care planning**, the goal of which is to help ensure that people receive medical care that is consistent with their values, goals and preferences during serious and chronic illness. ADs take effect when the patient can no longer communicate his or her preferences directly. While oral statements about these matters are ethically binding, they are not legally binding in all states. State-specific AD forms are available from a number of sources, including the National Hospice Palliative Care Organization (https://www.caringinfo.org/planning/advance-directives/) and Prepare for Your Care (prepareforyourcare.org).

Clinicians should address the core elements of advance care planning for all patients with serious illness—ideally, well before the end of life—to elicit their preferences, to appoint a surrogate, to talk to that person about their preferences, and to complete a formal AD. Most patients with a serious illness have already thought about end-of-life issues, want to discuss them with their clinician, want the clinician to bring up the subject, and feel better for having had the discussion. Patients who have such discussions with their clinicians are more satisfied with their clinician, are perceived by their family as having a better quality of life at the end of life, are less likely to die in the hospital, and are more likely to utilize hospice care. The loved ones of patients who engage in advance care planning discussions are less likely to suffer from depression during bereavement.

One type of AD is the **Durable Power of Attorney for Health Care (DPOA-HC)** that allows the patient to designate a surrogate decision maker. Identifying and documenting the surrogate decision maker may be the most important part of advance care planning. The DPOA-HC is particularly useful because it is often difficult to anticipate what specific decisions will need to be made. The responsibility of the surrogate is to provide "substituted judgment"—to decide as the *patient* would, not as the *surrogate* wants. Clinicians should encourage patients to talk with their surrogates about their preferences generally and about scenarios that are likely to arise, such as the need for mechanical ventilation in a patient with end-stage emphysema or in any patient with possible SARS-CoV-2 infection. In the absence of a designated surrogate, clinicians usually turn to family members or next of kin. In the United States, regulations require health care institutions to inform patients of their rights to formulate an AD. **Physician (or Medical) Orders for Life-Sustaining Treatment**

(POLST or MOLST) or **Physician (or Medical) Orders for Scope of Treatment (POST or MOST)** forms are clinician orders that document patient preferences and accompany patients wherever they are cared for—home, hospital, or nursing home. They are available in most states and used to complement ADs for patients approaching the end of life.

Gupta A et al. Value of advance care directives for patients with serious illness in the era of COVID pandemic: a review of challenges and solutions. Am J Hosp Palliat Care. 2021;38:191. [PMID: 33021094]
Hirakawa Y et al. Implementation of advance care planning amid the COVID-19 crisis: a narrative review and synthesis. Geriatr Gerontol Int. 2021;21:779. [PMID: 34318579]
Jones T et al. Advance care planning, palliative care, and end-of-life care interventions for racial and ethnic underrepresented groups: a systematic review. J Pain Symptom Manage. 2021;62:e248. [PMID: 33984460]

Do Not Attempt Resuscitation Orders

Because the "default" in US hospitals is that patients will undergo CPR in the event of cardiopulmonary arrest, clinicians should elicit patient preferences about CPR as a part of advance care planning. Most patients and many clinicians overestimate the chances of success of CPR. Only about 17% of all patients who undergo CPR in the hospital survive to hospital discharge and, among people with multisystem organ failure, metastatic cancer, or sepsis, the likelihood of survival to hospital discharge following CPR is virtually nil. Patients may ask their hospital clinician to write an order that CPR not be attempted should they experience cardiac arrest. Although this order initially was referred to as a **"DNR" (do not resuscitate)** order, many clinicians prefer the term **"DNAR" (do not attempt resuscitation)** to emphasize the low likelihood of success. Some clinicians and institutions use an order to **"Allow Natural Death"** for situations in which death is imminent and the patient wishes to receive only those interventions that will promote comfort.

For most patients at the end of life, decisions about CPR may not be about *whether* they will live but about *how* they will die. Clinicians should correct the misconception that withholding CPR in appropriate circumstances is tantamount to "not doing everything" or "just letting someone die." While respecting the patient's right to make the decision—and keeping in mind their own biases and prejudices—clinicians should offer explicit recommendations about DNAR orders and protect dying patients and their families from feelings of guilt and from the sorrow associated with vain hopes. Clinicians should discuss what interventions will be continued and started to promote quality of life rather than focusing only on what interventions will be stopped or not begun. For patients with implanted cardioverter defibrillators (ICDs), clinicians must also address the issue of turning off these devices, while leaving the pacemaker function on, as death approaches to prevent the uncommon but distressing situation of the ICD discharging during the dying process.

Kim C et al. The Do Not Resuscitate (DNR) order in the perioperative setting: practical considerations. Curr Opin Anaesthesiol. 2021;34:141. [PMID: 33630773]

CARE OF PATIENTS AT THE END OF LIFE

In the United States, more than 2.85 million people die each year. COVID-19 has emerged as a common cause of death both in the United States and around the world. Caring for patients at the end of life is an important responsibility and a rewarding opportunity for clinicians. From the medical perspective, the end of life may be defined as that time when death—whether due to terminal, acute or chronic illness—is expected within hours to months and can no longer be reasonably forestalled by medical intervention. Palliative care at the end of life focuses on relieving distressing symptoms and promoting quality of life, as it does in all other stages of illness. For patients at the end of life, palliative care may become the sole focus of care.

Prognosis at the End of Life

Clinicians must help patients understand when they are approaching the end of life. Most patients, and their family caregivers, want accurate prognostic information. This information influences patients' treatment decisions, may change how they spend their remaining time, and does *not* negatively impact patient survival. One-half or more of cancer patients do not understand that many treatments they might be offered are palliative and not curative.

While certain diseases, such as cancer, are more amenable to prognostic estimates, the other common causes of death—including heart disease, stroke, chronic lung disease, dementia, and COVID-19—have more variable trajectories and difficult-to-predict prognoses. Even for patients with cancer, clinician estimates of prognosis are often inaccurate and generally overly optimistic. The advent of new anticancer treatments including immunotherapy and targeted therapies has made prognosis more challenging in some cancers. Nonetheless, clinical experience, epidemiologic data, guidelines from professional organizations, and computer modeling and prediction tools (eg, the Palliative Performance Scale or http://eprognosis.ucsf.edu) may be used to offer patients more realistic estimates of prognosis. To determine whether a discussion of prognosis would be appropriate, clinicians can also ask themselves "Would I be surprised if this patient died in the next year?" If the answer is "no," then the clinician should initiate a discussion. Recognizing that patients may have different levels of comfort with prognostic information, clinicians can introduce the topic by simply saying, "I have information about the likely time course of your illness. Would you like to talk about it?"

Hui D et al. Prognostication in advanced cancer: update and directions for future research. Support Care Cancer. 2019;27:1973. [PMID: 30863893]
Wattanapisit S et al. Prognostic disclosure and quality of life in palliative care: a systematic review. BMJ Support Palliat Care. 2021;11:361. [PMID: 33257406]

Expectations About the End of Life

Death is often regarded by clinicians, patients, and families as a failure of medical science. This attitude can create or heighten a sense of guilt about the failure to prevent dying. Both the general public and clinicians often view death as an enemy to be battled furiously in hospitals rather than as an inevitable outcome to be experienced as a part of life at home. This idea contributes to the fact that most people in the United States die in hospitals or long-term–care facilities even though they may have wished otherwise. There is a trend of fewer deaths in hospitals and more deaths at home or in other community settings.

Relieving suffering, providing support, and helping the patient make the most of their life, or as a clinician might say to a patient, "helping you live as well as possible for as long as possible," should be foremost considerations, even when the clinician and patient continue to pursue cure of potentially reversible disease. Patients at the end of life and their families identify a number of elements as important to quality end-of-life care: managing pain and other symptoms adequately, avoiding inappropriate prolongation of dying, communicating clearly, preserving dignity, preparing for death, achieving a sense of control, relieving the burden on others, and strengthening relationships with loved ones.

Rosenberg A et al. Holding hope for patients with serious illness. JAMA. 2021;326:1259. [PMID: 34529011]

Communication & Care of the Patient at the End of Life

Caring for patients at the end of life requires the same skills clinicians use in other tasks of medical care: diagnosing treatable conditions, providing patient education, facilitating decision making, and expressing understanding and caring. Communication skills are vitally important and can be improved through training. Higher-quality communication is associated with greater satisfaction and awareness of patient wishes. Clinicians must become proficient at delivering serious news and then dealing with its consequences (Table 5–1). Smartphone and Internet communication resources are available to support clinicians (www.vitaltalk.org), and evidence suggests that communication checklists and guides can be effective. When the clinician and patient do not share a common language, the use of a professional interpreter is needed to facilitate clear communication and help broker cultural issues.

Three further obligations are central to the clinician's role at this time. First, he or she must work to identify, understand, and relieve physical, psychological, social, and spiritual distress or suffering. Second, clinicians can serve as facilitators or catalysts for hope. While hope for a particular outcome such as cure may fade, it can be refocused on what is *still* possible. Although a patient may hope for a "miracle," other more likely hopes can be encouraged and supported, including hope for relief of pain, for reconciliation with loved ones, for discovery of meaning, and for spiritual growth. With such questions as "What is still possible now for you?" and "When you look to the future, what do you hope for?" clinicians can help patients uncover hope, explore meaningful and realistic goals, and develop strategies to achieve them.

Finally, dying patients' feelings of isolation and fear demand that clinicians assert that they will care for the patient throughout the final stage of life. The *promise of nonabandonment* is the central principle of end-of-life care and is a clinician's pledge to serve as a caring partner, a resource for creative problem solving and relief of suffering, a guide during uncertain times, and a witness to the patient's experiences—no matter what happens. Clinicians can say to a patient, "I will care for you whatever happens."

Table 5–1. Suggestions for the delivery of serious news.

Prepare an appropriate place and time.
Address basic information needs.
Be brief and direct; avoid jargon and euphemisms.
Allow for silence and expression of emotions.
Assess and validate patient reactions.
Respond to immediate discomforts and risks.
Listen actively and express empathy.
Achieve a common perception of the problem.
Reassure that care will continue.
Ensure follow-up and make specific plans for the future.

Paladino J et al. Evaluating an intervention to improve communication between oncology clinicians and patients with life-limiting cancer: a cluster randomized clinical trial of the Serious Illness Care Program. JAMA Oncol. 2019;5:801. [PMID: 30870556]

Thodé M et al. Feasibility and effectiveness of tools that support communication and decision making in life-prolonging treatments for patients in hospital: a systematic review. BMJ Support Palliat Care. 2020 Oct 5. [Epub ahead of print] [PMID: 33020150]

Nutrition & Hydration

People approaching the end of life often lose their appetite and most stop eating and drinking in their last days. Clinicians should explain to families that the dying patient is not suffering from hunger or thirst; rather, the discontinuation of eating and drinking is part of dying, not its cause. The anorexia-cachexia syndrome frequently occurs in patients with advanced cancer, and cachexia is common and a poor prognostic sign in patients with heart failure. The associated ketonemia can produce a sense of well-being, analgesia, and mild euphoria. Although it is unclear to what extent withholding hydration at the end of life creates an uncomfortable sensation of thirst, any such sensation is usually relieved by simply moistening the dry mouth with ice chips, hard candy, swabs, or popsicles. Although this normal process of diminishing oral intake and accompanying weight loss is very common, it can be distressing to patients and families who may associate the offering of food with compassion and love and lack of eating with distressing images of starvation. In response, patients and families often ask about supplemental enteral or parenteral nutrition.

Supplemental artificial nutrition and hydration offer no benefit to those at the end of life and rarely achieve patient and family goals. The American Geriatrics Society recommends against artificial nutrition ("tube feeding") in people with advanced dementia because it does not provide any benefit. Furthermore, enteral feeding may cause nausea and vomiting in ill patients and can lead to diarrhea in the setting of malabsorption. Artificial nutrition and hydration may increase oral and airway secretions as well as increase the risk of choking, aspiration, and dyspnea; ascites, edema, and effusions may be worsened. In addition, artificial nutrition by nasogastric and gastrostomy tubes and parenteral nutrition impose risks of infection, epistaxis, pneumothorax, electrolyte imbalance, and aspiration—as well as the need to physically restrain the delirious patient to prevent dislodgment of tubes and catheters.

Individuals at the end of life have a right to voluntarily refuse all nutrition and hydration. Because they may have deep social and cultural significance for patients, families, and clinicians themselves, decisions about artificial nutrition and hydration are not simply medical. Eliciting perceived goals of artificial nutrition and hydration and correcting misperceptions can help patients and families make clear decisions.

Mayers T et al. International review of national-level guidelines on end-of-life care with focus on the withholding and withdrawing of artificial nutrition and hydration. Geriatr Gerontol Int. 2019;19:847. [PMID: 31389113]

Shih YA et al. Decision making of artificial nutrition and hydration for cancer patients at terminal stage—a systematic review of the views from patients, families, and healthcare professionals. J Pain Symptom Manage. 2021;62:1065. [PMID: 33933623]

Psychological, Social, & Spiritual Issues at the End of Life

Dying is not exclusively or even primarily a biomedical event. It is an intimate personal experience with profound psychological, interpersonal, and existential meanings. For many people at the end of life, the prospect of impending death stimulates a deep and urgent assessment of their identity, the quality of their relationships, the meaning and purpose of their life, and their legacy.

A. Psychological Challenges

Most patients at the end of life experience denial and isolation, anger, bargaining, depression, and acceptance but not in an orderly progression. In addition to these five reactions are the perpetual challenges of anxiety and fear of the unknown. Simple information, listening, assurance, and support may help patients with these psychological challenges. Patients and families rank emotional support as one of the most important aspects of good end-of-life care. Psychotherapy and group support may be beneficial as well.

Despite the significant emotional stress of facing death, clinical depression is *not* normal at the end of life and should be treated. Cognitive and affective signs of depression, such as feelings of worthlessness, hopelessness, or helplessness, may help distinguish depression from the low energy and other vegetative signs common with advanced illness. Although traditional antidepressant treatments such as SSRIs are effective, more rapidly acting medications, such as dextroamphetamine (2.5–7.5 mg orally at 8 AM and noon) or methylphenidate (2.5–10 mg orally at 8 AM and noon), may be particularly useful when the end of life is near or while waiting for another antidepressant medication to take effect. Ketamine is now approved, with restrictions, as a treatment for depression. Some research suggests a mortality benefit from treating depression in the setting of serious illness.

B. Social Challenges

At the end of life, patients should be encouraged to take care of personal, professional, and business obligations. These tasks include completing important work or personal projects, distributing possessions, writing a will, and making funeral and burial arrangements. The prospect of death often prompts patients to examine the quality of their interpersonal relationships and to begin the process of saying goodbye (Table 5–2). Concern about estranged relationships or "unfinished business" with significant others and interest in reconciliation may become paramount at this time.

C. Spiritual Challenges

Spirituality includes the attempt to understand or accept the underlying meaning of life, one's relationships to oneself and other people, one's place in the universe, one's legacy, and the possibility of a "higher power" in the universe. People may experience spirituality as part of or distinct from particular religious practices or beliefs.

The patient's spiritual concerns often require only a clinician's attention, listening, and witness. Clinicians can inquire about the patient's spiritual concerns and ask whether the patient wishes to discuss them. For example, asking, "How are you within yourself?" or "Are you at peace?" communicates that the clinician is interested in the patient's whole experience and provides an opportunity for the patient to share perceptions about his or her inner life. Questions that might constitute an existential "review of systems" are presented in Table 5–3. Formal legacy work and dignity therapy have been shown to be effective in improving quality of life and spiritual well-being.

Attending to the spiritual concerns of patients calls for listening to their stories. Storytelling may be facilitated by

Table 5–2. Five statements often necessary for the completion of important interpersonal relationships.

1. "Forgive me."	(An expression of regret)
2. "I forgive you."	(An expression of acceptance)
3. "Thank you."	(An expression of gratitude)
4. "I love you."	(An expression of affection)
5. "Goodbye."	(Leave-taking)

Source: Byock I. *Dying Well: Peace and Possibilities at the End of Life.* New York: Riverhead Books, an imprint of Penguin Group (USA) LLC, 1997.

Table 5–3. An existential review of systems.

Intrapersonal
"What does your illness/dying mean to you?"
"What do you think caused your illness?"
"How have you been healed in the past?"
"What do you think is needed for you to be healed now?"
"What is right with you now?"
"What do you hope for?"
"Are you at peace?"
Interpersonal
"Who is important to you?"
"To whom does your illness/dying matter?"
"Do you have any unfinished business with significant others?"
Transpersonal
"What is your source of strength, help, or hope?"
"Do you have spiritual concerns or a spiritual practice?"
"If so, how does your spirituality relate to your illness/dying, and how can I help integrate your spirituality into your health care?"
"What do you think happens after we die?"
"What do you think is trying to happen here?"

suggesting that the patient share his or her life story with family members, make an audio or video recording, assemble a photo album, organize a scrapbook, or write or dictate an autobiography.

The end of life offers an opportunity for psychological, interpersonal, and spiritual development and a chance to experience and achieve important goals. Individuals may grow—even experience a heightened sense of well-being or transcendence—in the process of dying. Through listening, support, and presence, clinicians may help foster this learning and be a catalyst for this transformation. Clinicians and patients may be guided by a developmental model of life that recognizes a series of lifelong developmental tasks and landmarks and allows for growth at the end of life.

Haufe M et al. How can existential or spiritual strengths be fostered in palliative care? An interpretative synthesis of recent literature. BMJ Support Palliat Care. 2020 Sep 14. [Epub ahead of print] [PMID: 32928785]

Lee W et al. Clinically significant depressive symptoms are prevalent in people with extremely short prognoses—a systematic review. J Pain Symptom Manage. 2021;61:143. [PMID: 32688012]

Cultural Issues

Various religious, ethnic, gender, class, and cultural traditions influence a patient's style of communication, comfort in discussing particular topics, expectations about dying and medical interventions, and attitudes about the appropriate disposition of dead bodies. While culture influences approaches to ADs, autopsy, organ donation, hospice care, and withdrawal of life-sustaining interventions, clinicians should be careful not to make assumptions about individual patients. Clinicians must appreciate that palliative care is susceptible to the same explicit and implicit biases documented in other medical disciplines. Being sensitive to a person's cultural beliefs and lived experiences and respecting traditions are important responsibilities of the clinician caring for a patient at the end of life. A clinician may ask a patient, "What do I need to know about you and your beliefs that will help me take care of you?" and "How do you deal with these issues in your family?"

Abdullah R et al. Preferences and experiences of Muslim patients and their families in Muslim-majority countries for end-of-life care: a systematic review and thematic analysis. J Pain Symptom Manage. 2020;60:1223. [PMID: 32659320]

De Souza J et al. Perspectives of elders and their adult children of Black and minority ethnic heritage on end-of-life conversations: a meta-ethnography. Palliat Med. 2020;34:195. [PMID: 31965907]

La IS et al. Palliative care for the Asian American adult population: a scoping review. Am J Hosp Palliat Care. 2021;38:658. [PMID: 32489147]

Wang SY et al. Racial differences in health care transitions and hospice use at the end of life. J Palliat Med. 2019;22:619. [PMID: 30615546]

Withdrawal of Curative Efforts

Requests from appropriately informed and competent patients or their surrogates for withdrawal of life-sustaining interventions must be respected. Limitation of life-sustaining interventions prior to death is common practice in ICUs in the United States. The withdrawal of life-sustaining interventions, such as mechanical ventilation, must be approached carefully to avoid patient suffering and distress for those in attendance. Clinicians should educate the patient and family about the expected course of events and the difficulty of determining the precise timing of death after withdrawal of interventions. Sedative and analgesic agents should be administered to ensure patient comfort even at the risk of respiratory depression or hypotension. While "death rattle," the sound of air flowing over airway secretions, is common in actively dying patients and can be distressing to families, it is doubtful that it causes discomfort to the patient. Turning the patient can decrease the sound of death rattle. Subcutaneous scopolamine butylbromide administered prophylactically can reduce death rattle. Suctioning should be avoided since it can cause patient discomfort.

McPherson K et al. Limitation of life-sustaining care in the critically ill: a systematic review of the literature. J Hosp Med. 2019;14:303. [PMID: 30794145]

van Esch HJ et al. Effect of prophylactic subcutaneous scopolamine butylbromide on death rattle in patients at the end of life: the SILENCE randomized clinical trial. JAMA. 2021;326:1268. [PMID: 34609452]

Hospice & Other Palliative Care Services

Hospice is a specific type of palliative care service that comprehensively addresses the needs of the dying, focusing on their comfort while not attempting to prolong their life or hasten their death. In the United States in 2018, 50.7% of people with Medicare who died used hospice, most at home or in a nursing home where they can be cared for by their family, other caregivers, and visiting hospice staff. Hospice care can also be provided in institutional residences and hospitals. As is true of all types of palliative care, hospice emphasizes individualized attention and

human contact with appropriate precautions for COVID-19 and uses an interdisciplinary team approach. Hospice care can include arranging for respite for family caregivers and assisting with referrals for legal, financial, and other services. Patients in hospice require a physician, preferably their primary care clinician or specialist, to oversee their care.

Based on 2019 data, hospice care was used by 1.49 million US Medicare beneficiaries, about 30% of whom had cancer. Hospice is rated highly by families and has been shown to increase patient satisfaction and to decrease family caregiver mortality. In 2018, 51% of hospice patients died at home; 30% died in a skilled nursing facility. Despite evidence suggesting that hospice care does not shorten length of life, hospice care tends to be engaged very late, often near the very end of life. In 2018, the mean average length of stay in hospice care in the United States was 90 days, but the median length of stay was 18 days. Overall, 54% of patients died within 30 days of enrolling in a hospice, and 28% of patients died within 7 days of starting hospice.

In the United States, most hospice organizations require clinicians to estimate the patient's prognosis to be less than 6 months, since this is a criterion for eligibility under the Medicare hospice benefit and is typically the same for other insurance coverage. Many patients wait to enroll in hospice until they have decided with certainty that they no longer wish to pursue curative intent treatment. This approach contributes to late referrals and to many patients missing out on valuable hospice services. Patients can be encouraged to enroll in hospice while they are still deciding about further curative intent treatment and can disenroll if they decide to pursue it.

Tobin J et al. Hospice care access inequalities: a systematic review and narrative synthesis. BMJ Support Palliat Care. 2021 Feb 19. [Epub ahead of print] [PMID: 33608254]

Medical Aid in Dying

Medical aid in dying is the legally sanctioned process by which patients who have a terminal illness may request and receive a prescription from a physician for a lethal dose of medication that the patients can self-administer for the purpose of ending their own life. Terminology for this practice varies. "Medical aid in dying" is used here to clarify that a willing physician provides assistance in accordance with the law (by writing a prescription for a lethal medication) to a patient who makes a request for it and who meets specific criteria. Patients, family members, nonmedical and medical organizations, clinicians, lawmakers, and the public frequently use other terms, such as "physician-assisted death," "aid in dying," "death with dignity," or "physician-assisted suicide." Use of the latter term is discouraged because when this action is taken according to the law, it is not considered suicide and people who are actively suicidal are not eligible for this process.

Although public and state support for medical aid in dying has grown in the United States, this remains an area of debate. As of 2021, medical aid in dying has been legalized with specific procedures for residents in the District of Columbia and nine US states (Oregon, Washington, Vermont, Colorado, Hawaii, Maine, New Jersey, California, and Montana [the Supreme Court in Montana ruled that the state constitution does not bar medical aid in dying]. This means that medical aid in dying is currently available to about one-fifth of the US population. Medical aid in dying remains illegal in all other states. Internationally, medical aid in dying (and/or euthanasia, the administration a lethal dose of medication by a clinician) is legal in nine countries (the Netherlands, Belgium, Luxembourg, Switzerland, Colombia, Canada, Germany, Japan, and the Australian state of Victoria). Current US state laws permitting medical aid in dying generally require physician certification of a terminal disease with a prognosis of 6 months or less and require the patient be an adult resident of the state, be physically capable of self-administering the medication, and be capable of making and communicating their own health care decisions. Any clinician that participates in medical aid in dying should be familiar with the laws governing its use in their jurisdiction and seek recommendations and help with writing the appropriate prescription.

Most requests for medical aid in dying come from patients with cancer; US patients requesting it are usually male, White, college-educated, and receiving hospice care. Requests for medical aid in dying are relatively rare, and ultimately, use of the prescribed medication led to less than 0.5% of all deaths in the United States. In Oregon, the first US state to legalize medical aid in dying, approximately 0.39% of deaths in 2015 resulted from this practice. In California in 2017, just 0.21% of people who died did so through medical aid in dying. Patient motivations for medical aid in dying generally revolve around preserving dignity, self-respect, and autonomy (control), and maintaining personal connections at the end of life rather than experiencing intolerable pain or suffering. Some patients who have requested medication later withdraw their request when provided palliative care interventions.

Each clinician must decide his or her personal approach in caring for patients who ask about medical aid in dying. Regardless of the clinician's personal feelings about the process, the clinician can respond initially by exploring the patient's reasons and concerns that prompted the request. During the dialog, the clinician should inform the patient about palliative options, including hospice care; access to expert symptom management; and psychological, social, and spiritual support, as needed, and should provide reassurance and commitment to address future problems that may arise. For clinicians who choose not to participate in medical aid in dying, referral to another clinician may be necessary, may be required by law, and may help the patient avoid feeling abandoned. The clinician referred to must be willing to provide the prescription for lethal medication, to care for the patient until death, to sign the death certificate listing the underlying terminal condition as the cause of death, and in some jurisdictions to complete a mandatory follow-up form.

Barsness JG et al. US medical and surgical society position statements on physician-assisted suicide and euthanasia: a review. BMC Med Ethics. 2020;21:111. [PMID: 33143695]

Gruenewald DA et al. Options of last resort: palliative sedation, physician aid in dying, and voluntary cessation of eating and drinking. Med Clin North Am. 2020;104:539. [PMID: 32312414]
Madadin M et al. The Islamic perspective on physician-assisted suicide and euthanasia. Med Sci Law. 2020;60:278. [PMID: 32623956]
Patel T. Clinician responses to legal requests for hastened death: a systematic review and meta-synthesis of qualitative research. BMJ Support Palliat Care. 2021;11:59. [PMID: 32601150]

Ethical & Legal Issues at the End of Life

Clinicians' care of patients at the end of life is guided by the same ethical and legal principles that inform other types of medical care. Foremost among these are (1) truth-telling, (2) nonmaleficence, (3) beneficence, (4) autonomy, (5) confidentiality, and (6) procedural and distributive justice. Important ethical principles may come into conflict when caring for patients. For example, many treatments that promote beneficence and autonomy, such as surgery or bone marrow transplantation, may violate the clinician's obligation for nonmaleficence; thus, balancing the benefits and risks of treatments is a fundamental ethical responsibility. While in most cases clinicians and patients and families will agree on the appropriateness of decisions to withdraw life-sustaining interventions, in rare cases, clinicians may determine *unilaterally* that a particular intervention, such as CPR in multisystem organ failure, offers no possibility of benefit and thus need not be done. In such cases, the clinician's intention to withhold CPR should be communicated to the patient and family and documented, and the clinician must consult with another clinician not involved in the care of the patient. If differences of opinion persist about the appropriateness of particular care decisions, consultation with an institutional ethics committee should be sought. Because such unilateral actions violate the autonomy of the patient, clinicians should *rarely* resort to them. Studies confirm that most disagreements between patients and families and clinicians can be resolved with good communication. Although clinicians and family members often feel differently about withholding versus withdrawing life-sustaining interventions, there is consensus among ethicists, supported by legal precedent, of their ethical equivalence. Regarding the aggressive treatment of pain and other distressing symptoms at the end of life, the ethical principle of **"double effect"** argues that properly informed patients or their surrogates pursuing interventions, even with the potential to hasten imminent death, is acceptable if the negative outcome comes as the known but unintended consequence of a primary intention to provide comfort and relieve suffering.

Arantzamendi M et al. Clinical aspects of palliative sedation in prospective studies. A systematic review. J Pain Symptom Manage. 2021;61:831. [PMID: 32961218]
Chessa F et al. Ethical and legal considerations in end-of-life care. Prim Care. 2019;46:387. [PMID: 31375188]
Ciancio AL et al. The use of palliative sedation to treat existential suffering: a scoping review on practices, ethical considerations, and guidelines. J Palliat Care. 2020;35:13. [PMID: 30757945]

Caring for the Family of Patients at the End of Life

Clinicians must be attuned to the potential impact of illness on the patient's family, including greater physical caregiving responsibilities and financial burdens as well as higher rates of anxiety, depression, chronic illness, and even mortality. The threatened loss of a loved one may create or reveal dysfunctional or painful family dynamics. Family caregivers, most often women, commonly provide the bulk of care for patients at the end of life, yet their work is often not adequately acknowledged, supported, or compensated. Clinicians should recognize that in many cases patients and their families are the unit of care. Simply acknowledging and praising the caregiver can provide much needed and appreciated support.

Clinicians can help families confront the imminent loss of a loved one but often must negotiate amid complex and changing family needs. Identifying a spokesperson for the family, conducting family meetings, allowing all to be heard, and providing time for consensus may help the clinician work effectively with the family. Telemedicine allows family members to participate in medical visits even if they are far away and to communicate with a loved one who is hospitalized, including in the setting of visitation restrictions imposed by COVID-19. Providing good palliative care to the patient can reduce the risk of depression and complicated grief in loved ones after the patient's death. Palliative care support directly to caregivers can prevent or improve caregiver depression.

Durepos P et al. What does death preparedness mean for family caregivers of persons with dementia? Am J Hosp Palliat Care. 2019;36:436. [PMID: 30518228]
Soikkeli-Jalonen A et al. Supportive interventions for family members of very seriously ill patients in inpatient care: a systematic review. J Clin Nurs. 2021;30:2179. [PMID: 33616267]

Clinician Self-Care When Patients Die or Are Dying

Many clinicians find caring for patients at the end of life to be one of the most rewarding aspects of practice. However, working with the dying is also sad and can invoke feelings of grief and loss in clinicians. It has been overwhelming for many in the COVID-19 pandemic. Clinicians must be able to tolerate the uncertainty, ambiguity, and existential challenges of such caregiving. Clinicians also need to recognize and respect their own limitations, attend to their own needs, and work in sustainable health care systems in order to avoid being overburdened, overly distressed, or emotionally depleted.

Horn DJ et al. Burnout and self care for palliative care practitioners. Med Clin North Am. 2020;104:561. [PMID: 32312415]
Imbulana DI et al. Interventions to reduce moral distress in clinicians working in intensive care: a systematic review. Intensive Crit Care Nurs. 2021;66:103092. [PMID: 34147334]
Medisauskaite A et al. Reducing burnout and anxiety among doctors: randomized controlled trial. Psychiatry Res. 2019; 274:383. [PMID: 30852432]

Zanatta F et al. Resilience in palliative healthcare professionals: a systematic review. Support Care Cancer. 2020;28:971. [PMID: 31811483]

TASKS AFTER DEATH

After the death of a patient, the clinician is called upon to perform a number of tasks, both required and recommended. The clinician must plainly and directly inform the family of the death, complete a death certificate, contact an organ procurement organization, and request an autopsy. Providing words of sympathy and reassurance, time for questions and initial grief and, for people who die in the hospital or other health care facility, a quiet private room for the family to grieve is appropriate and much appreciated.

The Pronouncement & Death Certificate

In the United States, state policies direct clinicians to confirm the death of a patient in a formal process called "pronouncement." The diagnosis of death is typically easy to make, and the clinician need only verify the absence of spontaneous respirations and cardiac activity by auscultating for each for 1 minute. A note describing these findings, the time of death, and that the family has been notified is entered in the patient's medical record. In many states, when a patient whose death is expected dies outside of the hospital (at home or in prison, for example), nurses may be authorized to report the death over the telephone to a physician who assumes responsibility for signing the death certificate within 24 hours. It is helpful to anticipate a death at home and inform families about what to do. They should be told that the death is not an emergency and that the family can spend time with their loved after death before calling a mortuary. For traumatic deaths, some states allow emergency medical technicians to pronounce a patient dead at the scene based on clearly defined criteria and with physician telephonic or radio supervision.

While the pronouncement may often seem like an awkward and unnecessary formality, clinicians may use this time to reassure the patient's loved ones at the bedside that the patient died peacefully and that all appropriate care had been given. Both clinicians and families may use the ritual of the pronouncement as an opportunity to begin to process emotionally the death of the patient.

Physicians are legally required to report certain deaths to the coroner and to accurately report the underlying cause of death on the death certificate. This reporting is important both for patients' families (for insurance purposes and the need for an accurate family medical history) and for the epidemiologic study of disease and public health. For example, it is important to understand the number of deaths due to COVID-19 and for clinicians to accurately report this cause of death. The physician should be specific about the major cause of death being the condition without which the patient would not have died (eg, "decompensated cirrhosis") and its contributory cause (eg, "hepatitis B and hepatitis C infections, chronic alcoholic hepatitis, and alcoholism") as well as any associated conditions (eg, "acute kidney injury")—and not simply put down "cardiac arrest" as the cause of death. In relevant cases, it is prohibited (in some jurisdictions) to list either "medical aid in dying" (or any synonymous term) or the medications used to accomplish it on the death certificate; instead, the clinician prescribing the lethal dose of medication for this purpose and following the patient until death must (in most jurisdictions) complete and submit a follow-up form and list the cause of death as the underlying condition that led to death.

Hatano Y et al. Physician behavior toward death pronouncement in palliative care units. J Palliat Med. 2018;21:368. [PMID: 28945507]

Autopsy & Organ Donation

Discussing the options and obtaining consent for autopsy and organ donation with patients prior to death is a good practice as it advances the principle of patient autonomy and lessens the responsibilities of distressed family members during the period immediately following the death. In the United States, federal regulations require that a designated representative of an organ procurement organization approach the family about organ donation because designated organ transplant personnel are more experienced and successful than treating clinicians at obtaining consent for organ donation from surviving family members. While most people in the United States support the donation of organs for transplants, organ transplantation is severely limited by the availability of donor organs. The families of donors experience a sense of reward in contributing, even through death, to the lives of others.

The results of an autopsy may help surviving family members and clinicians understand the exact cause of a patient's death and foster a sense of closure. Despite the use of more sophisticated diagnostic tests, the rate of unexpected findings at autopsy has remained stable, and thus, an autopsy can provide important health information to families. Pathologists can perform autopsies without interfering with funeral plans or the appearance of the deceased. A clinician–family conference to review the results of the autopsy provides a good opportunity for clinicians to assess how well families are grieving and to answer questions.

Madi-Segwagwe BC et al. Barriers and facilitators to eye donation in hospice and palliative care settings: a scoping review. Palliat Med Rep. 2021;2:175. [PMID: 34223518]

Follow-Up & Grieving

Proper care of patients at the end of life includes following up with surviving family members after the patient has died. Contacting loved ones by telephone or video telemedicine technology enables the clinician to assuage any guilt about decisions the family may have made, assess how families are grieving, reassure them about the nature of normal grieving, and identify complicated grief or depression. Clinicians can recommend support groups and counseling as needed. A card or telephone call from the clinician to the family days to weeks after the patient's death (and perhaps on the anniversary of the death) allows the

clinician to express concern for the family and the deceased. For patients dying during the COVID-19 pandemic, physical closeness, leave-taking, and bereavement rituals have been constrained by the need for social distancing.

After a patient dies, clinicians also grieve. Although clinicians may be relatively unaffected by the deaths of some patients, other deaths may cause feelings of sadness, loss, and guilt. These emotions should be recognized as the first step toward processing and healing them. Each clinician may find personal or communal resources that help with the process of grieving. Shedding tears, sharing with colleagues, taking time for reflection, and engaging in traditional or personal mourning rituals all may be effective. Attending the funeral of a patient who has died can be a satisfying personal experience that is almost universally appreciated by families and that may be the final element in caring well for people at the end of life.

Johannsen M et al. Psychological interventions for grief in adults: a systematic review and meta-analysis of randomized controlled trials. J Affect Disord. 2019;253:69. [PMID: 31029856]
Rabow MW et al. Witnesses and victims both: healthcare workers and grief in the time of COVID-19. J Pain Symptom Manage. 2021;62:647. [PMID: 33556494]
Wallace CL et al. Grief during the COVID-19 pandemic: considerations for palliative care providers. J Pain Symptom Manage. 2020;60:e70. [PMID: 32298748]

PAIN MANAGEMENT

TAXONOMY OF PAIN

The International Association for the Study of Pain (IASP) defines **pain** as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." **Acute pain** resolves within the expected period of healing and is self-limited. **Chronic pain** persists beyond the expected period of healing and is itself a disease state. In general, chronic pain is defined as extending beyond 3–6 months, although definitions vary in terms of the time period from initial onset of nociception. **Cancer pain** is in its own special category because of the unique ways neoplasia and its therapies (such as surgery, chemotherapy, immunotherapy or radiation therapy) can lead to burdensome pain. Finally, related to cancer pain, there is **pain at the end of life,** for which measures to alleviate suffering may take priority over promoting restoration of function.

Pain is a worldwide burden; across the globe, one in five adults suffers from pain. In 2010, members from 130 countries signed the Declaration of Montreal stating that access to pain management is a fundamental human right. The first CDC guidelines on opioid prescribing for chronic pain, including chronic noncancer pain, cancer pain, and pain at the end of life, were published in March of 2016, and continue to be updated.

Centers for Disease Control and Prevention (CDC). Opioid Prescribing Guideline Resources. 2021 Feb 16. https://www.cdc.gov/opioids/providers/prescribing/index.html
Dowell D et al. No shortcuts to safer opioid prescribing. N Engl J Med. 2019;380:2285. [PMID: 31018066]
National Institutes of Health (NIH). National Institute on Drug Abuse. Opioid Overdose Crisis. 2021 Mar 11. https://nida.nih.gov/drug-topics/opioids/opioid-overdose-crisis

ACUTE PAIN

Acute pain resolves within the expected period of healing and is self-limited. Common examples include pain from dental caries, kidney stones, surgery, or trauma. Management of acute pain depends on comprehending the type of pain (somatic, visceral, or neuropathic) and on understanding the risks and benefits of potential therapies. At times, treating the underlying cause of the pain (eg, dental caries) may be all that is needed, and pharmacologic therapies may not be required for additional analgesia. On the other hand, not relieving acute pain can have consequences beyond the immediate suffering. Inadequately treated acute pain can develop into chronic pain in some patients. This transition from acute to chronic pain (so-called "chronification" of pain) depends on the pain's cause, type, and severity and on the patient's age, psychological status, and genetics, among other factors. This transition is an area of increasing study because chronic pain leads to significant societal costs beyond the individual's experiences of suffering, helplessness, and depression. Emerging studies have shown that increased intensity and duration of acute pain may be correlated with a higher incidence of chronic pain, and regional anesthesia, ketamine, gabapentinoids, and cyclooxygenase (COX) inhibitors may be helpful for prevention of chronic postsurgical pain. These approaches are particularly important given concerns that exposure to opioids in the perioperative period can lead to chronic opioid dependence.

The Oxford League Table of Analgesics is a useful guide; for example, it lists the number-needed-to-treat for specific doses of various medications to relieve acute pain. NSAIDs or COX inhibitors are at the top of the list, with the lowest number-needed-to-treat. These medications can be delivered via oral, intramuscular, intravenous, intranasal, rectal, transdermal, and other routes of administration. They generally work by inhibiting COX-1 and -2. The primary limitation of the COX inhibitors is their side effects of gastritis; kidney dysfunction; bleeding; hypertension; and cardiovascular adverse events, such as MI or stroke. Ketorolac is primarily a COX-1 inhibitor that has an analgesic effect as potent as morphine at the appropriate dosage. Like most pharmacologic therapies, the limitation of COX inhibitors is that they have a "ceiling" effect, meaning that beyond a certain dose, there is no additional benefit.

Acetaminophen (paracetamol) is effective as a sole agent, or in combination with a COX inhibitor or an opioid in acute pain. Its mechanism of action remains undetermined but is thought to act centrally through mechanisms such as the prostaglandin, serotonergic, and opioid pathways. It is one of the most widely used and best tolerated analgesics; its primary limitation is hepatoxicity when given in high doses or to patients with underlying impaired liver function.

Postoperatively, **patient-controlled analgesia (PCA)** with intravenous morphine, hydromorphone, or another opioid can achieve analgesia faster and with less daily medication requirement than with standard "as needed" or even scheduled intermittent dosing. PCA has been adapted for use with oral analgesic opioid medications and for neuraxial delivery of both opioids and local anesthetics in the epidural and intrathecal spaces. The goal of PCA is to maintain a patient's plasma concentration of opioid in the "therapeutic window," between the minimum effective analgesic concentration and a toxic dose.

In order to prevent opioid use disorder and prolonged inappropriate opioid use, multimodal analgesia (including regional anesthesia) has been employed to decrease the need for postoperative opioids. Patients may undergo either neuraxial anesthesia with an epidural catheter, for example, or regional anesthesia with a nerve block with or without a catheter. These techniques are effective for both intraoperative pain and postoperative pain management and can diminish the need for both intraoperative and postoperative opioids.

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Kandarian BS et al. Updates on multimodal analgesia and regional anesthesia for total knee arthroplasty patients. Best Pract Res Clin Anaesthesiol. 2019;33:111. [PMID: 31272649]
Small C et al. Acute postoperative pain management. Br J Surg. 2020;107:e70. [PMID: 31903595]
Tubog TD. Overview of multimodal analgesia initiated in the perioperative setting. J Perioper Pract. 2021;31:191. [PMID: 32508237]

CHRONIC NONCANCER PAIN

Chronic noncancer pain may begin as acute pain that then fails to resolve and extends beyond the expected period of healing or it may be a primary disease state, rather than the symptom residual from another condition. Common examples of chronic noncancer pain include chronic low-back pain and arthralgias (often somatic in origin), chronic abdominal pain and pelvic pain (often visceral in origin), and chronic headaches, peripheral neuropathy, and postherpetic neuralgia (neuropathic origin). Chronic noncancer pain is common, with the World Health Organization estimating a worldwide prevalence of 20%. In the United States, 11% of adults suffer from chronic noncancer pain.

Chronic noncancer pain requires interdisciplinary management. Generally, no one therapy by itself is sufficient to manage such chronic pain. Physical or functional therapy and cognitive behavioral therapy have been shown to be the most effective for treating chronic noncancer pain, but other modalities including pharmacologic therapy, interventional modalities, and complementary/integrative approaches are useful in caring for affected patients.

Chronic low-back pain, a common chronic noncancer pain, causes more disability globally than any other condition. Chronic low-back pain includes spondylosis, spondylolisthesis, spinal canal stenosis (Chapter 24), and the "failed back surgery syndrome". Also referred to as the post-laminectomy pain syndrome, it can affect 10–40% of patients after lumbar spine surgery.

Evidence-based practice does *not* support the use of prolonged opioid therapy for chronic low-back pain.

Qaseem A et al. Nonpharmacologic and pharmacologic management of acute pain from non-low back, musculoskeletal injuries in adults: a clinical guideline from the American College of Physicians and American Academy of Family Physicians. Ann Intern Med. 2020;173:739. [PMID: 32805126]
Treede RD et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Disease (ICD-11). Pain. 2019;160:19. [PMID: 30586067]
Zhao L et al. Treatment of discogenic low back pain: current treatment strategies and future options—a literature review. Curr Pain Headache Rep. 2019;23:86. [PMID: 31707499]

CANCER PAIN

Cancer pain is unique in cause and in therapies. Cancer pain consists of both acute pain and chronic pain from the neoplasm itself and from the therapies associated with it, such as surgery, chemotherapy, radiation, and immunotherapy. In addition, patients with cancer pain may also have acute or chronic non–cancer-related pain.

Cancer pain includes somatic pain (eg, neoplastic invasion of tissue), visceral pain (eg, painful hepatomegaly from liver metastases), neuropathic pain (eg, neoplastic invasion of sacral nerve roots), or pain from a paraneoplastic syndrome (eg, peripheral neuropathy). Chemotherapy can cause peripheral neuropathies, radiation can cause neuritis or skin allodynia, surgery can cause persistent postsurgical pain, and immunotherapy can cause arthralgias.

Generally, patients with cancer pain may have multiple reasons for pain and thus benefit from a comprehensive and multimodal strategy. The WHO Analgesic Ladder, first published in 1986, suggests starting medication treatment with nonopioid analgesics, then weak opioid agonists, followed by strong opioid agonists. While opioid therapy can be helpful for a majority of patients living with cancer pain, therapy must be individualized depending on the individual patient, their family, and the clinician. For example, if one of the goals of care is to have a lucid and coherent patient, opioids may not be the optimal choice; interventional therapies such as implantable devices may be an option, weighing their risks and costs against their potential benefits. Alternatively, in dying patients, provided there is careful documentation of continued, renewed, or accelerating pain, use of opioid doses exceeding those recommended as standard for acute (postoperative) pain is acceptable.

One of the unique challenges in treating cancer pain is that it is often a "moving target," with disease progression and improvements or worsening pain directly stemming from chemotherapy, radiation, or immunotherapy. Therefore, frequent adjustments may be required to any pharmacologic regimen. Interventional approaches such as celiac plexus neurolysis and intrathecal therapy are well-studied and may be appropriate both for analgesia as well as reduction of side effects from systemic medications. Radiation therapy (including single-fraction external beam treatments) or radionuclide therapy (eg, strontium-89), which aims to decrease the size of both primary and metastatic disease, is one of the unique options for patients with pain from cancer.

Lau J et al. Interventional anesthesia and palliative care collaboration to manage cancer pain: a narrative review. Can J Anaesth. 2020;67:235. [PMID: 31571119]
Magee D et al. Cancer pain: where are we now? Pain Manag. 2019;9:63. [PMID: 30516438]
Swarm RA et al. Adult Cancer Pain, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17:977. [PMID: 31390582]

PAIN AT THE END OF LIFE

Pain is what many people say they fear most about dying, and pain at the end of life is consistently undertreated. Up to 75% of patients dying of cancer, heart failure, COPD, AIDS, or other diseases experience pain. In the United States, the Joint Commission includes pain management standards in its reviews of health care organizations and, in 2018, it began mandating that each hospital have a designated leader in pain management.

The ratio of risk versus benefit changes in end-of-life pain management. Harms from the use of opioid analgesics, including death, eg, from respiratory depression (rare), are perhaps less of a concern in patients approaching the end of life. In all cases, clinicians must be prepared to use appropriate doses of opioids in order to relieve this distressing symptom for these patients. Typically, for ongoing cancer pain, a long-acting opioid analgesic can be given around the clock with a short-acting opioid medication as needed for "breakthrough" pain.

PRINCIPLES OF PAIN MANAGEMENT

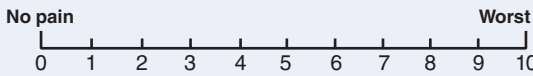
The experience of pain is unique to each person and influenced by many factors, including the patient's prior experiences with pain, meaning given to the pain, emotional stresses, and family and cultural influences. A brief means of assessing pain and evaluating the effectiveness of analgesia is to ask the patient to rate the degree of pain along a numeric or visual pain scale (Table 5–4), assessing trends over time. Clinicians should ask about the nature, severity, timing, location, quality, and aggravating and relieving factors of the pain.

General guidelines for diagnosis and management of pain are recommended for the treatment of all patients with pain but clinicians must comprehend that such guidelines may not be suited for every individual. Because of pain's complexity, it is important to understand benefits and risks of treatment with growing evidence for each patient. Distinguishing between nociceptive (somatic or visceral) and neuropathic pain is essential to proper management.

In addition, while clinicians should seek to diagnose the underlying cause of pain and then treat it, they must balance the burden of diagnostic tests or therapeutic interventions with the patient's suffering. For example, single-fraction radiation therapy for painful bone metastases or nerve blocks for neuropathic pain may obviate the need for ongoing treatment with analgesics and their side effects. Regardless of decisions about seeking and treating

Table 5–4. Pain assessment scales.

A. Numeric Rating Scale Verbal Intensity



None, mild, moderate, severe
(0), (1–4), (5–6), (7–10)

B. Numeric Rating Scale Translated into Word and Behavior Scales

Pain Intensity	Word Scale	Nonverbal Behaviors
0	No pain	Relaxed, calm expression
1–2	Least pain	Stressed, tense expression
3–4	Mild pain	Guarded movement, grimacing
5–6	Moderate pain	Moaning, restlessness
7–8	Severe pain	Crying out
9–10	Excruciating pain	Increased intensity of above

C. Wong-Baker FACES Pain Rating Scale[1]

[1]Especially useful for patients who cannot read English (and for pediatric patients).
Wong-Baker FACES Foundation (2015). Wong-Baker FACES® Pain Rating Scale. Retrieved with permission from http://www.WongBakerFACES.org.

the underlying cause of pain, every patient should be offered prompt pain relief.

The aim of effective pain management is to meet specific goals, such as preservation or restoration of function or quality of life, and this aim must be discussed between clinician and patient, as well as their family. For example, some patients may wish to be completely free of pain even at the cost of significant sedation, while others will wish to control pain to a level that still allows maximal cognitive functioning.

Whenever possible, the oral route of analgesic administration is preferred because it is easier to manage at home, is not itself painful, and imposes no risk from needle exposure. In unique situations, or near the end of life, transdermal, subcutaneous, rectal, and intravenous routes of administration are used; intrathecal administration is used when necessary.

Finally, pain management should not automatically indicate opioid therapy. While some individuals fare better with opioid therapy in specific situations, this does not mean that opioids are the answer for every patient. There are situations where opioids actually make the quality of life worse for individuals, due to a lack of adequate analgesic effect or due to their side effects.

Barriers to Good Care

One barrier to good pain control is that many clinicians have limited training and clinical experience with pain management and thus are reluctant to attempt to manage severe pain. Lack of knowledge about the proper selection and dosing of analgesic medications carries with it attendant and typically exaggerated fears about the side effects of pain medications. Consultation with a palliative care or a pain management specialist may provide additional expertise.

PHARMACOLOGIC PAIN MANAGEMENT STRATEGIES

Pain generally can be well controlled with nonopioid and opioid analgesic medications, complemented by nonpharmacologic adjunctive and interventional treatments. For mild to moderate pain, acetaminophen, aspirin, and NSAIDs (also known as COX inhibitors) may be sufficient. For moderate to severe pain, especially for those with acute pain, short courses of opioids are sometimes necessary; for those with cancer pain or pain from advanced, progressive serious illness, opioids are generally required and interventional modalities should be considered. In all cases, the choice of an analgesic medication must be guided by careful attention to the physiology of the pain and the benefits and risks of the particular analgesic being considered.

Acetaminophen, Aspirin, Celecoxib, & NSAIDs (COX Inhibitors)

Table 5–5 provides comparison information for acetaminophen, aspirin, the COX-2 inhibitor celecoxib and the NSAIDs. An appropriate dose of acetaminophen may be just as effective an analgesic and antipyretic as an NSAID but without the risk of GI bleeding or ulceration. Acetaminophen can be given at a dosage of 500–1000 mg orally every 6 hours, not to exceed 4000 mg/day maximum for short-term use. Total acetaminophen doses should not exceed 3000 mg/day for long-term use or 2000 mg/day for older patients and for those with liver disease. Hepatotoxicity is of particular concern because of how commonly acetaminophen is also an ingredient in various over-the-counter medications and because of failure to account for the acetaminophen dose in combination acetaminophen-opioid medications such as Vicodin or Norco. The FDA has limited the amount of acetaminophen available in some combination analgesics (eg, in acetaminophen plus codeine preparations).

Aspirin (325–650 mg orally every 4 hours) is an effective analgesic, antipyretic, and anti-inflammatory medication. GI irritation and bleeding are side effects that are lessened with enteric-coated formulations and by concomitant use of PPI medication. Bleeding, allergy, and an association with Reye syndrome in children and adolescents further limit its use.

NSAIDs are antipyretic, analgesic, and anti-inflammatory. Treatment with NSAIDs increases the risk of GI bleeding 1.5 times; the risks of bleeding and nephrotoxicity are both increased in elderly patients. GI bleeding and ulceration may be prevented with either the concurrent use of PPIs (eg, omeprazole, 20–40 mg orally daily) or the use of celecoxib (100 mg orally daily to 200 mg orally twice daily), the only COX-2 inhibitor available. Celecoxib and the NSAIDs can lead to fluid retention, kidney injury, and exacerbations of heart failure and should be used with caution in patients with that condition. Topical formulations of NSAIDs (such as diclofenac 1.3% patch or 1% gel), placed over the painful body part for treatment of musculoskeletal pain, are associated with less systemic absorption and fewer side effects than oral administration and are likely underutilized in patients at risk for GI bleeding.

Noori SA et al. Nonopioid versus opioid agents for chronic neuropathic pain, rheumatoid arthritis pain, cancer pain and low back pain. Pain Manag. 2019;9:205. [PMID: 30681031]

Opioids

A. Background

The 2019 National Health Interview Survey found that 20.5% of all Americans (50.2 million adults) suffer from chronic pain (defined as lasting 3 months or longer), with 11.2% of adults having daily pain. Roughly 20% of Americans who present to a primary care physician with noncancer pain receive a prescription for an opioid. There is moderate level randomized controlled trial evidence that opioids are effective in decreasing noncancer nociceptive pain lasting less than 3 months. However, there is no strong evidence to support use of opioids for management of chronic pain lasting longer than 3 months. The prevalence of opioid use is higher in men, those with chronic pain, those who are younger, and those with multiple prescription medications. One meta-analysis has estimated that in a cohort of patients utilizing opioids for chronic noncancer pain, one-third (36.3%) were doing so in a "problematic" fashion.

Table 5–5. Acetaminophen, aspirin, and useful NSAIDs and COX inhibitors.

Medication (Proprietary)	Usual Dose for Adults Based on Weight	Cost[1]	Comments[2]
Acetaminophen (Ofirmev)	≥ *50 kg:* 1000 mg intravenously every 6–8 hours	*Per unit:* $24.00 per vial of 1000 mg *For 30 days:* $2880.00	
Acetaminophen or paracetamol[3] (Tylenol, Datril, etc)	≥ *50 kg:* 325–500 mg orally every 4 hours or 500–1000 mg orally every 6 hours, up to 2000–4000 mg/day < *50 kg:* 10–15 mg/kg every 4 hours orally; 15–20 mg/kg every 4 hours rectally, up to 2000–3000 mg/day	*Per unit:* $0.02/500 mg (oral) OTC; $0.43/650 mg (rectal) OTC *For 30 days:* $3.60 (oral); $77.40 (rectal)	Not an NSAID because it lacks peripheral anti-inflammatory effects. Equivalent to aspirin as analgesic and antipyretic agent. Limit dose to 4000 mg/day in acute pain, and to 3000 mg/day in chronic pain. Limit doses to 2000 mg/day in older patients and those with liver disease. Be mindful of multiple sources of acetaminophen from combination analgesics, cold remedies, and sleep aids.
Aspirin[4]	≥ *50 kg:* 325–650 mg orally every 4 hours < *50 kg:* 10–15 mg/kg every 4 hours orally; 15–20 mg/kg every 4 hours rectally	*Per unit:* $0.02/325 mg OTC; $1.46/300 mg (rectal) OTC *For 30 days:* $7.20 (oral); $525.60 (rectal)	Available also in enteric-coated oral form that is more slowly absorbed but better tolerated.
Celecoxib[3] (Celebrex)	≥ *50 kg:* 200 mg orally once daily (OA); 100–200 mg orally twice daily (RA) < *50 kg:* 100 mg orally once or twice daily	*Per unit:* $4.37/100 mg; $7.57/200 mg *For 30 days:* $227.10 OA; $454.20 RA	Cyclooxygenase-2 inhibitor. No antiplatelet effects. Lower doses for elderly who weigh < 50 kg. Lower incidence of endoscopic GI ulceration than NSAIDs. Not known if true lower incidence of GI bleeding. Celecoxib is contraindicated in sulfonamide allergy.
Diclofenac (Flector)	≥ *50 kg:* 1.3% topical patch applied twice daily	*Per unit:* $14.92/patch *For 30 days:* $895.20	Apply patch to most painful area. Diclofenac 1% gel is available over the counter.
Diclofenac (Voltaren, Cataflam, others)	≥ *50 kg:* 50–75 mg orally two or three times daily; 1% gel 2–4 g four times daily	*Per unit:* $0.95/50 mg; $1.14/75 mg; $0.52/g gel *For 30 days:* $85.50; $102.60; $249.60 gel	May impose higher risk of hepatotoxicity. Enteric-coated product; slow onset. Topical formulations may result in fewer side effects than oral formulations.
Diclofenac sustained release (Voltaren-XR, others)	≥ *50 kg:* 100–200 mg orally once daily	*Per unit:* $2.70/100 mg *For 30 days:* $162.00	
Etodolac (Lodine, others)	≥ *50 kg:* 200–400 mg orally every 6–8 hours	*Per unit:* $1.32/400 mg *For 30 days:* $158.40	
Ibuprofen (Caldolor)	≥ *50 kg:* 400–800 mg intravenously every 6 hours	*Per unit:* $26.08/800 mg vial *For 30 days:* $3129.60	
Ibuprofen (Motrin, Advil, Rufen, others)	≥ *50 kg:* 400–800 mg orally every 6 hours < *50 kg:* 10 mg/kg orally every 6–8 hours	*Per unit:* $0.05/600 mg Rx; $0.02/200 mg OTC *For 30 days:* $6.00; $3.60	Relatively well tolerated and inexpensive.
Indomethacin (Indocin, Indometh, others)	≥ *50 kg:* 25–50 mg orally two to four times daily	*Per unit:* $0.38/25 mg; $0.64/50 mg *For 30 days:* $45.60; $76.80	Higher incidence of dose-related toxic effects, especially GI and bone marrow effects.
Ketorolac tromethamine	≥ *50 kg:* 10 mg orally every 4–6 hours to a maximum of 40 mg/day orally	*Per unit:* $2.16/10 mg *For 30 days:* Not recommended	Short-term use (< 5 days) only; otherwise, increased risk of GI side effects.
Ketorolac tromethamine[5]	≥ *50 kg:* 60 mg intramuscularly or 30 mg intravenously initially, then 30 mg every 6 hours intramuscularly or intravenously	*Per unit:* $1.19/30 mg *For 30 days:* Not recommended	Intramuscular or intravenous NSAID as alternative to opioid. Lower doses for elderly. Short-term use (< 5 days) only.

(*continued*)

Table 5–5. Acetaminophen, aspirin, and useful NSAIDs and COX inhibitors. (continued)

Medication (Proprietary)	Usual Dose for Adults Based on Weight	Cost[1]	Comments[2]
Magnesium salicylate (various)	≥ *50 kg:* 325–650 mg orally every 6 hours	*Per unit:* $0.25/325 mg OTC *For 30 days:* $60.00	
Meloxicam (Mobic)	≥ *50 kg:* 7.5 mg orally every 12 hours	*Per unit:* $2.78/7.5 mg *For 30 days:* $166.80	Intermediate COX-2/COX-1 ratio similar to diclofenac.
Nabumetone (Relafen)	≥ *50 kg:* 500–1000 mg orally once daily (max dose 2000 mg/day)	*Per unit:* $0.78/500 mg; $0.82/750 mg *For 30 days:* $46.80; $49.20	May be less ulcerogenic than ibuprofen, but overall side effects may not be less.
Naproxen (Naprosyn, Anaprox, Aleve [OTC], others)	≥ *50 kg:* 250–500 mg orally every 6–8 hours < *50 kg:* 5 mg/kg every 8 hours	*Per unit:* $1.26/500 mg Rx; $0.04/220 mg OTC *For 30 days:* $151.20; $3.60 OTC	Generally well tolerated. Lower doses for elderly.

OA, osteoarthritis; OTC, over the counter; RA, rheumatoid arthritis, Rx, prescription.
[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: IBM Micromedex® Red Book (electronic version). IBM Watson Health. Greenwood Village, Colorado, USA. Available at https://www-micromedexsolutions-com.proxy.hsl.ucdenver.edu/(cited March 11, 2022). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.
[2]The adverse effects of headache, tinnitus, dizziness, confusion, rashes, anorexia, nausea, vomiting, gastrointestinal bleeding, diarrhea, nephrotoxicity, visual disturbances, etc, can occur with any of these drugs. Tolerance and efficacy are subject to great individual variations among patients. Note: All NSAIDs can increase serum lithium levels.
[3]Acetaminophen and celecoxib lack antiplatelet effects.
[4]May inhibit platelet aggregation for 1 week or more and may cause bleeding.
[5]Has the same gastrointestinal toxicities as oral NSAIDs.

Since its beginning in the 1990s, an epidemic of opioid use and opioid overdose deaths has emerged to be a critical public health crisis in the United States. Based on provisional data from the CDC's National Center for Health Statistics, there were an estimated 100,306 overdose deaths in the United States in the 12-month period preceding April 2021; of these, 78,673 were attributed to opioids. There was a roughly 28.5% increase in overdose deaths when compared to the previous year. Among patients who are prescribed long-term opioid therapy, between 2% and 6% develop a substance use disorder. Roughly 11.7% of patients over the age of 12 have used an illicit drug in the last month.

Interestingly, the contribution of opioids to overdose deaths has changed over time and has been characterized by three "waves." In 1999, most opioid-related overdose deaths were attributed to prescription opioids ("wave 1"), but in 2010 there was a marked increase in heroin-related deaths ("wave 2"), and finally in 2013 there was a dramatic increase in synthetic opioid-related deaths ("wave 3").

Since 2010, the percentage of opioid overdose deaths associated with opioid prescriptions has steadily declined, and in 2019, only 28% of all opioid overdose deaths were associated with prescriptions. Instead, a massive increase in the illicit production of synthetic fentanyl (fentanyl and fentanyl analogs—either prescribed or illicitly manufactured and sold as counterfeit tablets or heroin) largely contributed to the third wave. From 2013 to 2019, the CDC reported a 1040% increase in synthetic opioid involved death rate; roughly half of overdose deaths in 2019 were attributed to synthetic opioids.

Population-based studies have also demonstrated that a sharp increase in concurrent opioid and benzodiazepine use which has led to an increase in the overall risk of opioid overdose.

Sadly, a "fourth wave" of high opioid overdose–related mortality is anticipated, driven by a foundation of illicit synthetic fentanyl and synergized with increasing methamphetamine and cocaine use, as well as the psychosocial stress of the COVID-19 pandemic.

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Centers for Disease Control and Prevention (CDC). National Center for Health Statistics. Provisional Drug Overdose Death Counts. 2022 Feb 16. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm
Centers for Disease Control and Prevention (CDC). Opioid Prescribing Guideline Resources. 2021 Feb 16. https://www.cdc.gov/opioids/providers/prescribing/index.html
Centers for Disease Control and Prevention (CDC). Prescription Opioid Overdose Death Maps. 2021 Mar 24. https://www.cdc.gov/drugoverdose/deaths/prescription/maps.html
Ciccarone D. The rise of illicit fentanyls, stimulants and the fourth wave of the opioid overdose crisis. Curr Opin Psychiatry. 2021;34:344. [PMID: 33965972]
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Mattson CL et al. Trends and geographic patterns in drug and synthetic opioid overdose deaths—United States, 2013–2019. MMWR Morb Mortal Wkly Rep. 2021;70:202. [PMID: 33571180]
Yong RJ et al. Prevalence of chronic pain among adults in the United States. Pain. 2022;163:e328. [PMID: 33990113]

B. Opioid Metabolism

Opioid medications mimic the pharmacologic properties of endogenous opioid peptides and activate the primary opioid receptors (mu, delta, and kappa). Additionally, the different opioid medications activate the different opioid

receptors to varying degrees. Any substance that causes analgesia via binding an opioid receptor and is reversed by naloxone is referred to as an "opioid." This broad class of drugs include alkaloids derived from the extract of a poppy plant (codeine and morphine) or synthetic peptides, both phenylpiperidines (eg, meperidine, fentanyl) and pseudopiperidines (eg, methadone).

Opioids are primarily metabolized by the liver via phase I (cytochrome P450 isoenzyme 3A4 and 2D6) and phase II (glucuronidation) processes. With advanced age, the following changes occur: hepatic blood flow decreases, systemic clearance of drugs decreases, elimination half-life increases, and the pharmacologic effect becomes longer. Such age-related changes in hepatic function predispose older individuals to adverse side effects from opioids, including delirium, falls, fractures, and respiratory depression. This predisposition seems to be dose-dependent—for example, individuals using greater than 50 oral morphine equivalents per day are twice as likely to suffer a fracture than those using less.

Opioid metabolism is also affected by kidney function. GFR typically decreases with age and a decrease in GFR can lead to an accumulation of active metabolites and consequent toxicity. For example, meperidine is metabolized to normeperidine and its accumulation results in neurotoxicity (seizures). Meperidine use should be avoided in older adults.

Therefore, clinicians should "start low and go slow," particularly in patients with older age, liver disease, decreased kidney function, and higher total body fat, when initiating opioid therapy. In addition, initially prescribing immediate-release opioid formulations is more desirable since these agents can be titrated down more rapidly in case of adverse reactions.

James A et al. Basic opioid pharmacology—an update. Br J Pain. 2020;14:115. [PMID: 32537150]

C. Principles of Opioid Management

Patients who suffer from opioid **addiction** continue to use the drug despite incurring harm. Often they are unable to fulfill work obligations or social roles yet they cannot control or decrease their opioid usage. Patients with opioid **pseudoaddiction** run out of their medication early and experience withdrawal symptoms. These patients are often undertreated but respond well to medication adjustment and typically do not require dose escalation once their medications are refilled on time correctly. Patients with opioid **dependence** have withdrawal symptoms with a rapid decrease or a stoppage of their opioid dosage. Patients afflicted with opioid **abuse** take the drug illicitly to obtain a "high" rather than for an analgesic or other medicinal purpose. Patients who have developed opioid **tolerance** have a decreased response to an opioid agonist with repeated use and will typically require increased dosages to achieve the same effect. Finally, utilization of high dosages of opioids over time can result in opioid-induced **hyperalgesia** (enhanced pain to noxious stimuli) and **allodynia** (pain from stimuli which typically do not provoke pain).

Once the decision has been made to prescribe an opioid, one of the initial challenges that a clinician may have is what dose to prescribe an opioid-naïve patient. Unlike most drugs, opioids have no ceiling effect for analgesia and a strategy for the management of future tolerance should be identified at the beginning. It is critical to calculate and understand the morphine milligram equivalent (MME) dose since adverse effects from opioids are dose-dependent (Table 5–6).

Table 5–6. Morphine milligram equivalent (MME) doses for commonly prescribed opioids.

Opioid	Conversion Factor
Morphine	1
Codeine	0.15
Fentanyl transdermal (in mcg/h)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1–20 mg/day	4
21–40 mg/day	8
41–60 mg/day	10
≥ 61–80 mg/day	12
Oxycodone	1.5
Oxymorphone	3

TO CALCULATE MMEs: Multiply the dose for each opioid by the conversion factor to determine the dose in MMEs. As an example: tablets containing hydrocodone 5 mg and acetaminophen 300 mg taken four times a day would contain a total of 20 mg of hydrocodone daily, equivalent to 20 × 1 = 20 MME daily. Or another example: Extended-release tablets containing oxycodone 10 mg taken twice a day contain a total of 20 mg of oxycodone daily, equivalent to 20 × 1.5 = 30 MME daily.

Note the following precautions: (1) All doses are in mg/day except for fentanyl, which is in mcg/hour. (2) Equianalgesic dose conversions are only estimates and cannot account for individual variability in genetics and pharmacokinetics. (3) Do not use the calculated dose in MMEs to determine the doses to use when converting one opioid to another; when converting opioids, the new opioid is typically dosed at a substantially lower dose than the calculated MME dose to avoid accidental overdose due to incomplete cross-tolerance and individual variability in opioid pharmacokinetics. (4) Use particular caution with methadone dose conversions because the conversion factor increases at higher doses. (5) Use particular caution with fentanyl because it is dosed in mcg/hour instead of mg/day, and its absorption is affected by heat and other factors.

From Dowell D et al. CDC guideline for prescribing opioids for chronic pain—United States, 2016. MMWR Recomm Rep. 2016;65(No. RR-1):1. [PMID: 26987082]. Adapted by the CDC from Von Korff M et al. De Facto long-term opioid therapy for noncancer pain. Clin J Pain. 2008;24:521 and Washington State Interagency Guideline on Prescribing Opioids for Pain. (http://www.agencymeddirectors.wa.gov/Files/2015AMDGO pioidGuideline.pdf) and from Yaksh T et al. Table 20-8. Opioids, Analgesia, and Pain Management. In: Brunton LL et al (editors). *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e.* McGraw Hill, 2018. Accessed November 22, 2021.

Adverse events are proportionately related to higher dosages. A population-based study that analyzed 607,156 patients prescribed opioids characterized the relationship between opioid dose and opioid overdose–related mortality. The adjusted OR for opioid overdose–related death increased from 1.32 (0.94–1.84) for patients prescribed between 20 and 50 MME/day to 1.92 (1.30–2.85) for those prescribed between 50 and 99 MME/day. In the same study, patients prescribed 200 MME/day or more had an OR of 2.88 (1.79–4.63) or a nearly threefold increase in the likelihood of death related to opioid overdose.

In other studies, rates of opioid abuse or dependence on long-term opioid therapy have ranged from 0.7% for patients prescribed 36 MME/day or less to 6.1% for those prescribed 120 MME/day or more. Prescribers must therefore remember that the risks of opioid overdose–related mortality substantially increases with dosages 50 MME/day or more. By contrast, studies have shown that initial opioid prescriptions for opioid-naïve patients of less than 50 MME/day have decreased risks of opioid overdose–related death. Recommended initial opioid dosing of selected opioid medications are shown in Table 5–7.

A particular challenge for clinicians is the management of the patient who presents in follow-up with inadequate pain control after the initial opioid prescription. Dose escalation performed within the first year of prescription has been associated with higher rates of substance abuse and more frequent non–face-to-face encounters. Men are at higher risk for dose escalation and opioid-related death than women. Dose escalation also increases the risk of overdose and subsequent development of opioid use disorder. Patients taking an MME dose of 200/day or more are at a particularly high risk for death from overdose.

Prescribers must therefore keep in mind that opioid overdose risk is dose dependent. Options for the patient with inadequate pain control after an initial opioid prescription include (1) increase the dosage, (2) use an extended-release version of the same drug with immediate-release medication for "breakthrough" pain, (3) add an adjuvant analgesic (eg, a muscle relaxant) or NSAID, (4) perform an opioid rotation, or (5) refer to a pain management specialist.

Once tolerance develops, clinicians who use only one opioid at a time (eg, morphine extended-release coupled with morphine immediate-release) can readily switch to an alternative opioid. In contrast, clinicians who use multiple different opioid agents (eg, morphine extended-release coupled with hydromorphone for breakthrough pain) have already used drugs targeting multiple opioid subreceptors at the same time and therefore have limited future possible opioid rotations once tolerance develops. Nonetheless, it is far more desirable to perform an opioid rotation than to escalate the dosage, which may result in adverse side effects (respiratory depression, constipation, urinary hesitancy, etc). Dose escalation is further undesirable as it may contribute to opioid-induced hyperalgesia, complicating future treatments and response to analgesics.

Clinicians must also carefully characterize the temporal patterns of pain when prescribing opioids. The astute clinician should discriminate between acute or "incident related" pain (pain experienced with activity but not at rest) and chronic pain (occurs at rest). Those with acute pain may be a better candidate for an immediate-release opioid formulation. Most opioid prescriptions (greater than 97%) are for immediate-release formulations; chronic pain patients are more likely to be prescribed extended-release formulations. However, patients who are prescribed extended-release opioids for their initial prescriptions have a higher risk of overdose compared to those prescribed immediate-release opioids.

Extended-release formulations offer a more convenient method of dosing, have a prolonged peak therapeutic drug range, less plasma level fluctuations, and improved compliance. Both extended- and immediate-release formulations pose significant risk of misuse and abuse. Reported immediate-release abuse has been linked to the perceived immediacy of relief. However, immediate-release formulations are easier to titrate and wean and seem a simpler choice when initiating an opioid prescription in opioid-naïve patients. Regardless of the final choice of agent, clinicians should characterize the temporal patterns of the pain and weigh the pros and cons of immediate- versus extended-release preparations. Key factors in the final choice include the length of the treatment plan, the minimally adequate MME dose, and the proposed length of opioid treatment.

Currently, there is no high-level evidence that supports the use of opioids in the long-term management of neuropathic pain. Instead, opioids have been found to have significantly more adverse effects when compared to neuropathic medications (Table 5–8).

Cuménal M et al. The safety of medications used to treat peripheral neuropathic pain, Part 2 (opioids, cannabinoids, and other drugs): review of double-blind, placebo-controlled, randomized clinical trials. Expert Opin Drug Saf. 2021;20:51. [PMID: 33103931]

Nalamachu SR et al. Abuse of immediate-release opioids and current approaches to reduce misuse, abuse, and diversion. Postgrad Med. 2018;1. [PMID: 30025214]

D. Adverse Effects of Opioids

Common adverse effects of opioids include constipation, nausea, sedation, pruritus, sexual dysfunction (especially hypogonadism in men), respiratory depression, and CNS depression. Core strategies to decrease adverse effects include performing an opioid rotation, dose reduction, change in route of administration (eg, from oral to transdermal), and symptom management.

Opioid-induced respiratory depression constitutes a medical emergency and must be managed appropriately. Though potentially fatal, it can be rapidly reversed by the opioid receptor antagonist, naloxone. There is moderate evidence that naloxone, when administered appropriately, can decrease opioid overdose–related mortality. However, out-of-hospital naloxone use is linked with opioid withdrawal syndrome. Naloxone-induced withdrawal can lead to cardiovascular events (increases in heart rate, mean arterial pressure, and cardiac index) as well as to pulmonary edema. Despite the risk, the CDC recommends coprescribing

Table 5–7. Opioids.

Medication (Proprietary)	Routes of Administration and Available Doses	Approximate Equianalgesic Dose (compared to morphine 30 mg orally or 10 mg intravenously/ subcutaneously)[1]	Usual Starting Dose in an Opioid-Naïve Patient Based on Weight	Cost
Opioid Agonists[2,3]				
Buprenorphine (Buprenex)[4]	*Parenteral* (intravenous, intramuscular)	300 mcg intravenously slowly once, may be repeated after 30–60 minutes once; or 600 mcg intramuscularly once	≥ *50 kg:* 300 mcg intravenously slowly once, may be repeated after 30–60 minutes once; or 600 mcg intramuscularly once	$14.77/300 mcg
Buprenorphine (Butrans)	*Transdermal:* 5, 7.5, 10, 15, and 20 mcg/h	Not available	≥ *50 kg:* Initiate 5 mcg/h patch for opioid-naïve patients (may currently be using nonopioid analgesics)	$114.77/10 mcg/h
Buprenorphine (Belbuca)	*Sublingual strips:* 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg	Not available	≥ *50 kg:* In opioid-naive or opioid-intolerant patients, individualize dose every 12 h. Start: 75 mcg buccally every 12–24 hours for at least 4 days, then increase to 150 mcg buccally every 12 hours, then may increase by no more than 150 mcg buccally every 12 hours no more frequently than every 4 days. Maximum: 900 mcg/12 hours	$7.69/75 mcg
Fentanyl	*Parenteral* (intravenous, intramuscular): 50 mcg/mL	*Parenteral:* 100 mcg every hour	≥ *50 kg:* 50–100 mcg intravenously/intramuscularly every hour or 0.5–1.5 mcg/kg/h intravenous infusion < *50 kg:* 0.5–1 mcg/kg intravenously every 1–4 hours or 1–2 mcg/kg intravenously × 1, then 0.5–1 mcg/kg/h infusion	$0.80/100 mcg
Fentanyl (Actiq)	*Transmucosal strips:* 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg	Not available	*Initial dose:* ≥ *50 kg:* 200 mcg	$18.80/200 mcg
Fentanyl (Fentora)	*Buccal:* 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg	Not available	*Initial dose:* ≥ *50 kg:* 100 mcg	$103.90/200 mcg
Fentanyl (Duragesic)	*Transdermal:* 12.5 mcg/h, 25 mcg/h, 37.5 mcg/h, 50 mcg/h, 62.5 mcg/h, 75 mcg/h, 87.5 mcg/h, 100 mcg/h	Conversion to fentanyl patch is based on total daily dose of oral morphine:[2] morphine 60–134 mg/day orally = fentanyl 25 mcg/h patch; morphine 135–224 mg/day orally = fentanyl 50 mcg/h patch; morphine 225–314 mg/day orally = fentanyl 75 mcg/h patch; and morphine 315–404 mg/day orally = fentanyl 100 mcg/h patch	*Initial doses:* ≥ *50 kg:* 12.5–25 mcg/h patch every 72 hours < *50 kg:* 12.5–25 mcg/h patch every 72 hours	$14.42/25 mcg/h

(*continued*)

Table 5–7. Opioids. (continued)

Medication (Proprietary)	Routes of Administration and Available Doses	Approximate Equianalgesic Dose (compared to morphine 30 mg orally or 10 mg intravenously/ subcutaneously)[1]	Usual Starting Dose in an Opioid-Naïve Patient Based on Weight	Cost
Hydromorphone[5] (Dilaudid)	*Oral:* 2 mg, 4 mg, 8 mg	*Oral:* 7.5 mg every 3–4 hours	*Oral:* ≥ *50 kg:* 1–2 mg every 3–4 hours < *50 kg:* 0.06 mg every 3–4 hours	$0.11/2 mg
	Parenteral (intravenous, intramuscular, subcutaneous): 0.5 mg/0.5 mL, 1 mg/mL, 2 mg/mL, 4 mg/mL	*Parenteral:* 1.5 mg every 3–4 hours	*Parenteral:* ≥ *50 kg:* 1.5 mg every 3–4 hours < *50 kg:* 0.015 mg/kg every 3–4 hours	$1.90/2 mg
Hydromorphone extended release	*Oral:* 8 mg ER, 12 mg ER, 16 mg ER, 32 mg ER	*Oral:* 45–60 mg ER every 24 hours	*Oral, initial dose:* ≥ *50 kg:* 8 mg ER every 24 hours	$9.24/8 mg
Levorphanol	*Oral:* 2 mg	*Oral:* 4 mg every 6–8 hours	*Oral, initial dose:* ≥ *50 kg:* 1–2 mg every 6–8 hours < *50 kg:* 0.04 mg/kg every 6–8 hours	$53.40/2 mg
Meperidine[6] (Demerol)	*Oral:* 50 mg, 100 mg	*Oral:* 300 mg every 2–3 hours; usual dose 50–150 mg every 3–4 hours	*Oral:* Not recommended	$5.22/100 mg
	Parenteral (intravenous, intramuscular, subcutaneous): 25 mg/mL, 50 mg/mL, 75 mg/mL, 100 mg/mL	*Parenteral:* 100 mg every 3 hours	*Parenteral:* ≥ *50 kg:* 50–100 mg every 3 hours; not to exceed 600 mg/24 h < *50 kg:* 0.75 mg/kg every 2–3 hours	$7.68/100 mg
Methadone (Dolophine, others)	*Oral:* 5 mg, 10 mg	*Oral:* 10–20 mg every 6–8 hours (when converting from < 100 mg long-term daily oral morphine[7])	*Oral, initial dose:* ≥ *50 kg:* 2.5–20 mg every 8–12 hours < *50 kg:* 0.2 mg/kg every 8–12 hours	$0.10/10 mg
	Parenteral: 10 mg/mL	*Parenteral:* 5–10 mg every 6–8 hours	*Parenteral:* ≥ *50 kg:* 2.5–10 mg every 6–8 hours < *50 kg:* 0.1 mg/kg every 6–8 hours	$21.00/10 mg
Morphine[5] immediate release (morphine sulfate, various)	*Oral:* 15 mg, 30 mg (tablets); 10 mg/5mL, 20 mg/5 mL, 100 mg/5 mL (solution) *Rectal:* 5 mg, 10 mg, 20 mg, 30 mg (suppositories)	*Oral:* 30 mg every 3–4 hours (around-the-clock dosing); 60 mg every 3–4 hours (single or intermittent dosing) *Rectal:* 10–20 mg per rectum every 4 hours	*Oral:* ≥ *50 kg:* 4–8 mg every 3–4 hours; used for breakthrough pain in patients already taking controlled-release preparations < *50 kg:* 0.3 mg/kg every 3–4 hours	$0.49/15 mg tablet; $0.84/20 mg oral solution
		Parenteral: 10 mg every 3–4 hours	*Parenteral:* ≥ *50 kg:* 10 mg every 3–4 hours < *50 kg:* 0.1 mg/kg every 3–4 hours	$4.89/10 mg
Morphine controlled release (MS Contin)	*Oral (tablets):* 15 mg ER, 30 mg ER, 60 mg ER, 100 mg ER, 200 mg ER	*Oral:* 90–120 mg ER every 12 hours	*Oral, initial dose:* ≥ *50 kg:* 15–60 mg ER every 8–12 hours	$0.73/30 mg
Morphine extended release (Kadian)	*Oral (capsules):* 10 mg ER, 20 mg ER, 30 mg ER, 40 mg ER, 50 mg ER, 60 mg ER, 80 mg ER, 100 mg ER, 200 mg ER	*Oral:* 180–240 mg ER every 24 hours	*Oral, initial dose:* ≥ *50 kg:* 30 mg ER every 24 hours	$5.69/30 mg

Oxycodone (Roxicodone, OXYIR)	*Oral:* *(capsules):* 5 mg IR *(tablets):* 5 mg IR, 10 mg IR, 15 mg IR, 20 mg IR, 30 mg IR	*Oral:* 20–30 mg every 3–4 hours	*Oral, initial dose:* ≥ *50 kg:* 5–10 mg every 3–4 hours < *50 kg:* 0.2 mg/kg every 3–4 hours	$0.08/5 mg
Oxycodone controlled release (Oxycontin)	*Oral:* *(tablets):* 10 mg ER, 15 mg ER, 20 mg ER, 30 mg ER, 40 mg ER, 60 mg ER, 80 mg ER *(solution):* 5 mg/mL, 100 mg/mL	*Oral:* 40 mg ER every 12 hours	*Oral, initial dose:* > *50 kg:* 10–40 mg ER every 12 hours	$10.43/20 mg
Oxycodone ER tamper-resistant capsules (Xtampza ER)	*Oral (capsules):* 9 mg ER, 13.5 mg ER, 18 mg ER, 27 mg ER, 36 mg ER	*Oral:* 36 mg every 12 hours	*Oral, initial dose:* 9 mg ER every 12 hours	$13.25/18 mg
Oxymorphone[5,8] oral, immediate release	*Oral (tablets):* 5 mg, 10 mg	*Oral:* 10 mg every 6 hours	*Oral, initial dose:* ≥ *50 kg:* 10–20 mg every 6 hours	$0.39/5 mg
Oxymorphone[5,8] oral, extended release	*Oral (tablets):* 5 mg ER, 7.5 mg ER, 10 mg ER, 15 mg ER, 20 mg ER, 30 mg ER, 40 mg ER	*Oral:* 30 mg every 12 hours	*Oral, initial dose:* ≥ *50 kg:* 5 mg ER orally every 12 hours	$14.88/20 mg
Combination Opioid Agonist–Nonopioid Preparations				
Codeine[9,10] (with acetaminophen or aspirin)	*Oral (tablets):* Acetaminophen with codeine phosphate (Tylenol #3) 300 mg/30 mg Acetaminophen with codeine phosphate (Tylenol #4) 300 mg/60 mg Aspirin 325 mg/codeine phosphate 30 mg Aspirin 325/codeine phosphate 60 mg	Not used secondary to acetaminophen or aspirin containing component	*Oral:* ≥ *50 kg:* 60 mg codeine phosphate every 4–6 hours < *50 kg:* 0.5–1 mg/kg every 3–4 hours	$0.64/60 mg
		Parenteral: 130 mg every 3–4 hours	*Parenteral:* ≥ *50 kg:* 60 mg codeine phosphate every 2 hours intramuscularly/subcutaneously; not available in the United States < *50 kg:* Not recommended	Not available in the United States
Hydrocodone[8] (with acetaminophen in Lortab)[11]	*Oral (solution):* 10 mg/300 mg per 15 mL *Oral (tablets):* 2.5 mg/325 mg, 5 mg/325 mg, 7.5 mg/325 mg, 10 mg/325 mg	Not used secondary to acetaminophen component	*Oral:* ≥ *50 kg:* 10 mg every 3–4 hours < *50 kg:* 0.2 mg/kg every 3–4 hours	$0.41/5 mg
Oxycodone (with acetaminophen)[10,11]	*Oral (tablets):* 2.5 mg/325 mg, 5 mg/325 mg, 7.5 mg/325 mg, 10 mg/325 mg	Not used secondary to acetaminophen component	*Oral, initial dose:* ≥ *50 kg:* 5–10 mg every 3–4 hours < *50 kg:* 0.2 mg/kg every 3–4 hours	$0.08/5 mg
Combination Opioid Agonist–Norepinephrine Reuptake Inhibitor Preparations				
Tapentadol (Nucynta)	*Oral (tablets):* 50 mg, 75 mg, 100 mg	Not available; use starting doses	*Oral, initial doses:* ≥ *50 kg:* Start 50–100 mg once, may repeat dose in 1 hour. Can increase to 50–100 mg every 4 hours. Maximum daily dose 600 mg	$14.36/100 mg

(*continued*)

Table 5–7. Opioids. (continued)

Medication (Proprietary)	Routes of Administration and Available Doses	Approximate Equianalgesic Dose (compared to morphine 30 mg orally or 10 mg intravenously/ subcutaneously)[1]	Usual Starting Dose in an Opioid-Naïve Patient Based on Weight	Cost
Tapentadol, extended release (Nucynta ER)	*Oral:* 50 mg ER, 100 mg ER, 150 mg ER, 200 mg ER, 250 mg ER	Not available; use starting doses	*Oral:* ≥ *50 kg:* Start 50 mg ER every 12 hours. Can increase by 50-mg increments twice daily every 3 days to dose of 100–250 mg ER twice daily	$16.71/100 mg
Tramadol	*Oral (tablets):* 50 mg, 100 mg	Not available	*Oral, initial dose:* ≥ *50 kg:* Start 25 mg orally daily. Can increase by 25 mg every 3 days to 25 mg orally 4 times daily, then may increase by 50 mg/day every 3 days to 100 mg orally 4 times daily. Limit of 300 mg/day in patients > 75 years old	$0.83/50 mg
Tramadol extended release (Conzip ER capsules)	*Oral (tablets):* 100 mg ER, 200 mg ER, 300 mg ER	Not available	*Oral, initial dose:* ≥ *50 kg:* 100 mg ER orally once daily, may titrate up by 100 mg increments every 5 days, max 300 mg	$19.35/200 mg

[1]Published tables vary in the suggested doses that are equianalgesic to morphine. Clinical response is the criterion that must be applied for each patient; titration to clinical efficacy is necessary. Because there is not complete cross-tolerance among these drugs, it is usually necessary to use a lower than equianalgesic dose initially when changing drugs and to retitrate to response.
[2]Conversion is conservative; therefore, do not use these equianalgesic doses for converting back from fentanyl patch to other opioids because they may lead to inadvertent overdose. Patients may require breakthrough doses of short-acting opioids during conversion to transdermal fentanyl.
[3]Several significantly more potent formulations of buprenorphine are available but generally reserved for the treatment of opioid use disorder with or without comorbid constant pain, most often by pain management specialists: a sublingual tablet (Subutex and others) or a sublingual film (Suboxone and others) in which the buprenorphine is combined with naloxone; a subdermal implant of buprenorphine alone (Probuphine); and a subcutaneous depot injection (Sublocade). Each of these is used in maintenance treatment to reduce problematic use of other opioids. See text.
[4]In opioid-experienced patients, taper current opioids to 30 mg/day oral morphine equivalent prior to starting buprenorphine. Thereafter, buprenorphine dosing schedule depends on prior current oral morphine equivalent:
< 30 mg/day, 75 mcg buccally every 12 hours;
30–89 mg/day, 150 mcg buccally every 12 hours;
90–160 mg/day, 300 mcg buccally every 12 hours;
In all patients, use same dose escalation and maximum dose as shown for opioid-naïve patients.
[5]*Caution:* For morphine, hydromorphone, and oxymorphone, rectal administration is an alternative route for patients unable to take oral medications. Equianalgesic doses may differ from oral and parenteral doses. A short-acting opioid should normally be used for initial therapy.
[6]Not recommended for chronic pain. Doses listed are for brief therapy of acute pain only. Switch to another opioid for long-term therapy.
[7]Methadone conversion varies depending on the equivalent total daily dose of morphine. Consult with a pain management or palliative care expert for conversion.
[8]*Caution:* Recommended doses do not apply to adult patients with kidney or liver impairment or other conditions affecting drug metabolism.
[9]*Caution:* Individual doses of codeine above 60 mg often are not appropriate because of diminishing incremental analgesia with increasing doses but continually increasing nausea, constipation, and other side effects.
[10]*Caution:* Doses of aspirin and acetaminophen in combination products must also be adjusted to the patient's body weight.
[11]*Caution:* Monitor total acetaminophen dose carefully, including any OTC use. Total acetaminophen dose maximum 3 g/day. If liver impairment or heavy alcohol use, maximum is 2 g/day. Available dosing formulations of these combination medications are being adjusted to reflect increased caution about acetaminophen toxicity. Acetaminophen doses in a single combination tablet or capsule will be limited to no more than 325 mg.
Note: Average wholesale price (AWP, generic when available) for quantity listed. Source: IBM Micromedex® Red Book (electronic version) IBM Watson Health. Greenwood Village, Colorado, USA. Available at https://www-micromedexsolutions-com.proxy.hsl.ucdenver.edu/ (cited March 15,2022). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

Table 5–8. Pharmacologic management of neuropathic pain.

Medication[1]	Starting Dose	Typical Dose
Antidepressants[2]		
Nortriptyline	10 mg orally at bedtime	10–150 mg orally at bedtime
Amitriptyline	10 mg orally at bedtime	10–150 mg orally at bedtime
Desipramine	12.5 mg orally at bedtime	12.5–250 mg orally at bedtime (can be divided into two doses)
Calcium Channel Alpha2-Delta Ligands		
Gabapentin[3]	100–300 mg orally once to three times daily	300–1200 mg orally three times daily
Pregabalin[4]	50 mg orally three times daily	50–150 mg orally three times daily
Selective Serotonin Norepinephrine Reuptake Inhibitors		
Duloxetine	30–60 mg orally daily or 20 mg orally twice daily in elders	60–120 mg orally daily
Venlafaxine[5]	75 mg orally daily divided into two or three doses	150–225 mg orally daily divided into two or three doses
Opioids	**(see Table 5–7)**	**(see Table 5–7)**
Topical and Other Medications		
Lidocaine transdermal	4% or 5% patch applied daily, for a maximum of 12 hours	1–3 patches applied daily for a maximum of 12 hours
Diclofenac transdermal	1.3% patch or 1% gel	Patch applied twice daily or gel applied three times daily
Tramadol hydrochloride[6]	50 mg orally four times daily	100 mg orally two to four times daily

[1]Begin at the starting dose and titrate up every 4 or 5 days. Within each category, drugs listed in order of prescribing preference.
[2]Begin with a low dose. Use the lowest effective dose. Pain relief may be achieved at doses below antidepressant doses, thereby minimizing adverse side effects. Do not combine with serotonin or norepinephrine reuptake inhibitors.
[3]Common side effects include nausea, somnolence, and dizziness. Must adjust dose for kidney impairment.
[4]Common side effects include dizziness, somnolence, peripheral edema, and weight gain. Must adjust dose for kidney impairment.
[5]*Caution:* Can cause hypertension and ECG changes. Consider obtaining baseline ECG and monitor.
[6]Tramadol is classified by the DEA as a Schedule IV controlled substance.

naloxone in patients who are receiving opioids of 50 MME/day or higher, who have a respiratory condition, who are concomitantly prescribed benzodiazepines, who have a history of substance abuse disorder, or who are otherwise at high risk for overdose.

Naloxone products approved by the US FDA include generic naloxone vials for injection and naloxone for intranasal administration.

Naloxone is typically administered intravenously; however, it can be administered subcutaneously, intramuscularly, or intranasally. The medication is titrated with the objective of improving the patient's respiratory function. Initial dosages usually range from 0.4 mg to 1.0 mg intravenously, though larger dosages (eg, 1.0 to 2.0 mg intravenously) may be used, even in patients without a history of opioid dependency. Apneic or cyanotic patients may require an even larger initial dosage. Naloxone generic is available in prefilled syringes containing 2 mg of naloxone per 2 mL for intramuscular, subcutaneous, or intravenous administration. The 2-mg dose is five times the original dosage when the medication was first approved; this is intended to counteract the effects of highly potent synthetic opioids. Narcan® Nasal Spray is now available in a prepackaged nasal spray with a 4 mg per actuation dosage; it is available in most US states for purchase directly from a pharmacist without a clinician's prescription. In addition, in 2021 the FDA approved Zimhi® 5 mg per 0.5 mL in prefilled syringes for injection. More recently in 2021, the FDA approved an even higher dosage (8 mg per actuation) of naloxone nasal spray (Kloxxado®) to combat overdose deaths related to the even more potent synthetic opioids.

Opioid-induced constipation is the most common adverse effect of opioids. Opioids bind to mu receptors in the GI tract and decrease bowel motility, secretions, and blood flow in a dose-related fashion. Ideally, patients treated with opioids will have a bowel movement at least every 24–48 hours. Initial recommendations for management of opioid-induced constipation should include patient education, increase in dietary fiber, adequate hydration, and regular physical activity. In addition, one successful approach combines laxatives (eg, Miralax®) along with a stimulant (eg, senna). Newer peripherally acting mu receptor antagonists (eg, naldemedine, naloxegol, and methylnaltrexone) block the GI actions of opioids without decreasing the opioid's analgesic effects. A recent meta- analysis has demonstrated promising effects, with a desired outcome of 3 or more bowel movements per week.

Roughly, 25% of patients prescribed opioids will develop nausea, likely secondary to direct stimulation of the chemoreceptor trigger zone, or to vestibular sensitivity,

or to decreased GI motility. Management options include antipsychotics (eg, prochlorperazine or promethazine), prokinetic agents (eg, metoclopramide), serotonin antagonists (eg, ondansetron), or antihistamines (eg, diphenhydramine or meclizine). All these agents have side effects that must be carefully monitored.

Between 20% and 60% of patients treated with opioids report sedation or decreased cognition, most commonly with initiation of opioid therapy or with dose escalation. Nonpharmacologic management of minor sedation includes caffeinated beverages. Pharmacologic management options include methylphenidate; however, high-level evidence supporting its use for this indication is lacking. Cognitive impairment (delirium) may be managed with low-dose haloperidol, perhaps a first choice due to to its lower incidence of cardiovascular and anticholinergic effects.

Pruritus occurs in 2–10% of patients given opioids, likely secondary to peripheral histamine release. Management options include an opioid rotation, dose reduction, diphenhydramine, and cool compresses.

Centers for Disease Control and Prevention (CDC). Stop overdose: lifesaving naloxone. 2022 Feb 23. https://www.cdc.gov/stopoverdose/naloxone/

Lyden J et al. The United States opioid epidemic. Semin Perinatol. 2019;43:123. [PMID: 30711195]

Ouyang R et al. Efficacy and safety of peripherally acting mu-opioid receptor antagonists for the treatment of opioid-induced constipation: a Bayesian network meta-analysis. Pain Med. 2020;21:3224. [PMID: 32488259]

US Department of Health and Human Services. How to respond to an opioid overdose. 2020 Sep 25. https://www.hhs.gov/opioids/treatment/overdose-response/index.html

E. CDC Guidelines

In 2016, the CDC established guidelines for prescribing opioids for chronic pain. Nonpharmacologic therapy and nonopioid pharmacologic treatments should be undertaken prior to initiation of opioids. Then, only patients who benefit with improved pain and function outweighing the risks of opioids should be considered as candidates for ongoing opioids. Furthermore, nonopioid management options including physical therapy should be used concomitantly. Additionally, the patient's medication history should be reviewed through their state prescription drug monitoring program prior to the initial prescription and periodically thereafter.

Clinicians should avoid opioids, or cautiously titrate the opioid dosage in patients with a history of heart failure, obesity, COPD, or sleep apnea. In pregnant women, opioids can pose some risks to the mother and fetus, including poor fetal growth, stillborn delivery, birth defects, and neonatal withdrawal syndrome. It is highly recommended that appropriate referral to clinicians with expertise in pain management be made for these patients.

When initiating therapy for acute pain, the CDC recommends using immediate-release formulations, at the lowest effective dose, initially for a limited period of 3–7 days. Patients should have close follow-up after the initial prescription, typically within 4 weeks. Risks and benefits should be analyzed, particularly in patients prescribed greater than 50 MME/day. Patients who have risk factors for opioid overdose (eg, history of substance abuse or previous overdose, high opioid dose [greater than 50 MME/day], or current benzodiazepine dose) may also be offered naloxone. Patients should not be prescribed opioids and benzodiazepines concurrently. The CDC guidelines for prescribing opioids for chronic pain are summarized in Table 5–9.

Table 5–9. CDC guidelines for prescribing opioids for chronic pain.

	Guideline
Risk assessment	Nonpharmacologic and nonopioid pharmacologic therapy are preferred; weigh risks and benefits of opioids for pain and function Establish treatment goals and consider how opioids will be discontinued if benefits do not outweigh the risks Prior to starting opioid therapy, discuss risks, benefits, and responsibilities with the patient When starting opioid therapy, prescribe immediate-release opioids instead of extended release for acute (eg, "breakthrough") pain
Opioid selection and dosage	When starting opioids, prescribe the lowest effective opioid dose, carefully weigh risks if dose is > 50 MME/day and avoid doses > 90 MME/day For acute pain, prescribe the lowest effective dose, and limit duration: ≤ 3 days should be sufficient and > 7 days will rarely, if ever, be needed
Monitoring	Evaluate benefits and harms within 1–4 weeks of starting opioids or of any dose escalations, then again at least every 3 months (or sooner). If benefits do not outweigh harms, clinicians should lower dosages of opioids or taper to discontinue opioids Periodically evaluate risk factors for opioid-related harms; offer naloxone for patients with risk factors such as history of substance abuse or overdose, high opioid dose (> 50 MME/day) or concurrent benzodiazepine prescription Review the patient's history of controlled substance use through their state's prescription drug monitoring program Perform urine drug testing when initiating opioids and then periodically (randomly) during treatment Avoid prescribing opioids and benzodiazepines concurrently Manage or arrange treatment for opioid use disorder, typically with methadone or buprenorphine combined with behavioral therapy

Adapted from: Dowell D, Haegerich TM, Chou R. CDC Guideline for prescribing opioids for chronic pain—United States, 2016. MMWR Recomm Rep. 2016;65:1.
MME, morphine milligram equivalent.

Centers for Disease Control and Prevention (CDC). Urine drug testing factsheet. https://www.cdc.gov/opioids/providers/prescribing/pdf/Urine-Drug-Testing-508.pdf
Federal Register, Vol. 86, No. 121, June 28, 2021. Registration requirements for narcotic treatment programs with mobile components. https://www.federalregister.gov/documents/2021/06/28/2021-13519/registration-requirements-for-narcotic-treatment-programs-with-mobile-components.

F. Basics of Monitoring

Prior to the initial opioid prescription, it is prudent to clearly define the underlying condition, diagnostic workup, nonopioid therapeutic management plan and intended length of prescription. Ideally, the prescriber should determine how the opioid prescription fits into a broader comprehensive pain management plan. The Opioid Risk Tool (available at https://www.drugabuse.gov/sites/default/files/files/OpioidRiskTool.pdf) should be administered to understand the risk (low, moderate, or high) for future opioid abuse.

Standardized assessments such as the "PEG" scores may be used at initial and follow-up visits to gauge the efficacy of treatment (Table 5–10).

The primary goal of opioid monitoring initiatives is to improve patient compliance with the opioid prescription. Monitoring programs have been shown to improve compliance, reduce hospitalizations, and decrease specialty referrals. Although there is weak to moderate evidence to support the efficacy of opioid monitoring (urine drug testing and prescription drug monitoring programs) and treatment agreements, such interventions are considered to be standard care and to represent the best opioid prescription practices.

Most controlled substance agreements have integral components that address topics such as the goals of treatments, medical risks of opioid use, illicit use, polypharmacy, and diversion. Such agreements are ideally "patient-centric" and involve a mutual agreement between the clinician and the patient. Important topics such as safety, adverse side effects, dangers of polypharmacy, and concomitant alcohol or benzodiazepine use are typically reviewed. The prescribing clinician needs to assure that the patient understands and agrees to the agreement prior to prescribing the opioid. Potential risks of opioid use must be discussed and documented, including addiction, respiratory depression, overdose, and death.

The CDC recommends that all patients receiving long-term opioid therapy have periodic urine drug tests, at least annually. It is critical to convey to the patient that a urine drug test does not mean a lack of trust but is a standard safety measure for all patients who are prescribed long-term opioids. Patients should understand that urine drug tests may be conducted randomly and repeatedly during treatment. Immunoassays are less expensive and screen for a panel of drugs, but these tests do not differentiate between opioids, have low sensitivity, and typically miss semisynthetic opioids (eg, hydrocodone and oxycodone) and synthetic opioids (eg, fentanyl and tramadol). In contrast, although liquid chromatography/mass spectrometry tests are more expensive and must be performed in a laboratory, these tests are far more sensitive, differentiate between all opioids, and are more accurate for semisynthetic and synthetic opioids.

Finally, the treatment agreement also represents an ideal time to discuss the warning signs of overdose and what steps the patient must take if these were to occur. Although no formal guidelines for concomitant naloxone prescription have been established, an increasing number of clinicians are writing a naloxone prescription along with the opioid for patients who are deemed at high risk for accidental overdose.

Patients who are noncompliant with an agreed-upon opioid management schedule may eventually be good candidates for an opioid taper, but this must be done with caution and patience. Abrupt discontinuation of an opioid has been shown to have potential disastrous consequences, including withdrawal, suicide, and self-medication with illicit narcotics. It is critical to have a well thought out strategy for opioid reduction and cessation that uses a safe transition to nonopioid pain management techniques, including utilization of nonopioid analgesics, adjuvant analgesics, physical therapy, and mental health counseling.

Table 5–10. PEG score to gauge benefit from long-term opioid use.

During the past week:
1. What number best describes your *P*ain? 0 = no pain to 10 = worst pain imaginable
2. What number best describes how much your pain interfered with your *E*njoyment of life? 0 = no interference to 10 = complete interference
3. What number describes how much pain interfered with your *G*eneral activity? 0 = no interference to 10 = complete interference

To calculate PEG score, average scores from questions 1 through 3. *Source:* https://www.cdc.gov/drugoverdose/pdf/pdo_checklist-a.pdf

Asamoah-Boaheng M et al. Interventions to influence opioid prescribing practices for chronic noncancer pain: a systematic review and meta-analysis. Am J Prev Med. 2021;60:e15. [PMID: 33229143]
Centers for Disease Control and Prevention (CDC). Urine Drug Testing Factsheet. https://www.cdc.gov/opioids/providers/prescribing/pdf/Urine-Drug-Testing-508.pdf
Covington EC et al. Ensuring patient protections when tapering opioids: consensus panel recommendations. Mayo Clin Proc. 2020;95:2155. [PMID: 33012347]

G. Management of Opioid Use Disorder

The FDA has approved several medications to manage opioid use disorder, including naltrexone, methadone, and buprenorphine. Naltrexone is an opioid antagonist that binds opioid receptors without activating them. Thus, use of naltrexone medication entails no risk of abuse or addiction. Naltrexone is prescribed orally or administered as an injectable to decrease the likelihood of relapse and to

increase treatment retention. However, studies validating its efficacy have been mixed.

Methadone (a full opioid receptor agonist) and buprenorphine (a partial opioid receptor agonist) have long half-lives and have been shown to decrease withdrawal syndromes, decrease opioid cravings, decrease illicit drug use, and decrease all-cause mortality. Despite reasonable evidence for their efficacy, these medications are underutilized, possibly because of a lack of patient and clinician education, appropriate clinician training, or patient social stigma of being prescribed these drugs.

Both methadone and buprenorphine require special clinician training and certification to prescribe them for opioid use disorder. Recently, however, efforts have been made to improve access to them for patients. While both drugs carry a risk of abuse, buprenorphine is less addictive than methadone. The Drug Addiction Treatment Act of 2000 allows for waivered physicians to prescribe buprenorphine but despite this Act, less than half of the counties in rural areas of the United States have buprenorphine providers. In 2021, the US Drug Enforcement Administration (DEA) authorized preexisting DEA registrants to add a mobile component to allow for better access for patients in underserved and rural areas. As a result, narcotic treatment programs no longer need to have a separate registration at each principal place of business where substances are dispensed.

Federal Register, Vol. 86, No. 121, June 28, 2021. Registration requirements for narcotic treatment programs with mobile components. https://www.federalregister.gov/documents/2021/06/28/2021-13519/registration-requirements-for-narcotic-treatment-programs-with-mobile-components

Lyden J et al. The United States opioid epidemic. Semin Perinatol. 2019;43:123. [PMID: 30711195]

H. Weaning from Opioids

The goals of appropriately tapering opioids are to minimize symptoms and signs of opioid withdrawal while weaning. Common withdrawal symptoms and signs of withdrawal include anxiety, drug craving, tachycardia, vomiting, diarrhea, and mydriasis. Guidelines have suggested that a 10% decrease in opioid dosage per week is reasonable. However, a more rapid taper over 3 weeks may be appropriate in cases of adverse events such as overdose. Conversely, a slower wean of a 10% decrease in opioid dosage per month is also reasonable and may be better tolerated. Nonopioid management of pain (eg, by physical therapy, cognitive behavioral therapy, adjuvant analgesics, and nonopioid analgesics) should be maximized during the period of weaning.

Moss C et al. Weaning from long-term opioid therapy. Clin Obstet Gynecol. 2019;62:98. [PMID: 30601171]

Medications for Neuropathic Pain

When taking a patient's history, listening for pain descriptions such as "burning," "shooting," "pins and needles," or "electricity," and for pain associated with numbness is essential because such a history suggests neuropathic pain.

Table 5–11. Medications used for treatment of peripheral neuropathic pain.

Type of Medication	Numbers Needed to Treat (NNT) for Peripheral Neuropathies Compared to NSAIDs
Tricyclic antidepressants	2.1
Opioids	2.6
Cannabinoids	3.4
Pregabalin	4.5
Tramadol	4.9
Duloxetine	5.1
Capsaicin 0.04%	6.2
Gabapentin	6.5
SSRIs	6.8

Data from Moulin D et al; Canadian Pain Society. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag. 2014;19:328.

Studies are mixed with regard to efficacy of opioids for neuropathic pain. However, a number of nonopioid medications have also been found to be effective in randomized trials (Table 5–8). Successful management of neuropathic pain often requires the use of more than one effective medication. Since these medications bind to receptors on a large variety of neurons, they often have CNS side effects. These side effects often limit reaching therapeutic doses and may be the reason for higher numbers needed to treat (NNT 4–7) as compared to NSAIDs (NNT 2–4) (Table 5–11).

The calcium channel alpha2-delta ligands, gabapentin and pregabalin, are first-line therapies for neuropathic pain. Both medications have no significant medication interactions. However, they can cause sedation, dizziness, ataxia, and GI side effects. Both gabapentin and pregabalin require dose adjustments in patients with kidney dysfunction. Gabapentin should be started at low dosages of 100–300 mg orally once daily and titrated upward by 300 mg/day every 4–7 days by adding additional doses throughout the day with a typical effective dose of 1800–3600 mg/day in three divided doses. Pregabalin should be started at 40–150 mg/day in two or three divided doses. If necessary, the dose of pregabalin can be titrated upward to 300–600 mg/day in two or three divided doses. Both medications are relatively safe in accidental overdose and may be preferred over tricyclic antidepressants (TCAs) for a patient with a history of heart failure or arrhythmia or if there is a risk of suicide. Prescribing both gabapentin and an opioid for neuropathic pain may provide better analgesia at lower doses than if each is used as a single agent.

The SNRIs duloxetine and venlafaxine are also first-line treatments for neuropathic pain. Patients should be advised to take duloxetine on a full stomach because nausea is a common side effect. Duloxetine may provide increased benefit for neuropathic pain up to a total daily dose of

120 mg, beyond the 60-mg limit used for depression. Duloxetine generally should not be combined with other serotonin or norepinephrine uptake inhibitors, but it can be combined with gabapentin or pregabalin. Lower doses of venlafaxine have more serotonin than norepinephrine activity; therefore, higher doses may be required to treat neuropathic pain. Because venlafaxine can cause hypertension and induce ECG changes, patients with cardiovascular risk factors should be carefully monitored when starting this medication. Desvenlafaxine, the active metabolite of venlafaxine, is also available and may be tolerated better than venlafaxine.

TCAs are another class of medications for neuropathic pain that work through the norepinephrine and serotonin pathways. Among the TCAs that are effective for neuropathic pain, nortriptyline and desipramine are preferred over amitriptyline because they cause less orthostatic hypotension and have fewer anticholinergic effects. Start with a low dosage (10–25 mg orally daily) and titrate upward in 10-mg increments every 4 or 5 days aiming to use the lowest effective dose and to titrate up to a maximum of no greater than 100 mg daily. It may take several weeks for a TCA to have its full analgesic effect for neuropathic pain. Because TCAs and SNRIs both work through the serotonin and norepinephrine pathways, they generally should not be co-prescribed, particularly due to concerns for the serotonin syndrome.

Topical medications, such as lidocaine 5% patch and capsaicin 8% patches, are considered second-line therapies. The lidocaine 5% patch is particularly effective in postherpetic neuralgia and may be effective in other types of localized neuropathic pain. Due to its relatively minimal adverse effects, it is commonly used despite being considered second line. Topical lidocaine 4% patches and cream are available over the counter. Other medications effective for neuropathic pain include tramadol and tapentadol, both of which are opioids with norepinephrine activity. Medical cannabis strains high in cannabidiol have proven efficacy for some types of neuropathic pain.

Szok D et al. Therapeutic approaches for peripheral and central neuropathic pain. Behav Neurol. 2019;2019:8685954. [PMID: 31871494]

Adjuvant Pain Medications & Treatments

If pain cannot be controlled without intolerable medication side effects, clinicians should consider using lower doses of multiple medications, which is done commonly for neuropathic pain, rather than larger doses of one or two medications.

For metastatic bone pain, the anti-inflammatory effect of NSAIDs can be helpful. Furthermore, bisphosphonates (such as pamidronate and zoledronic acid) and receptor activator of NF-kappa-B ligand (RANKL) inhibitors (such as denosumab) may relieve such bone pain, although they are generally more useful for prevention of bone metastases than for analgesia.

Corticosteroids, such as dexamethasone, prednisone, and methylprednisolone, can be helpful for patients with headache due to increased intracranial pressure, pain from spinal cord compression, metastatic bone pain, and neuropathic pain due to invasion or infiltration of nerves by tumor. Because of the side effects of long-term corticosteroid administration, they are most appropriate for short-term use and in patients with end-stage disease. Low-dose intravenous, oral, buccal, and nasal ketamine has been used successfully for neuropathic and other pain syndromes refractory to opioids, although research data are limited.

PSYCHOLOGICAL, PHYSICAL, & INTEGRATIVE THERAPIES

Psychological Therapy

Nonpharmacologic and noninterventional therapies are valuable in treating pain. In fact, cognitive behavioral therapy and physical or functional therapy have been shown to be the most effective for management of chronic pain. In multiple randomized, controlled studies, cognitive behavioral therapy has been proven effective as a primary evidence-based treatment for chronic pain. Because mood and psychological issues play an important role in the patient's perception of and response to pain, psychotherapy, support groups, prayer, and pastoral counseling can also help in pain management. Depression and anxiety, which may be instigated by chronic pain or may alter the response to pain, should be treated aggressively with antidepressants and anxiolytics.

Urits I et al. An update on cognitive therapy for the management of chronic pain: a comprehensive review. Curr Pain Headache Rep. 2019;23:57. [PMID: 31292747]

Physical Therapy

Physical therapy is a mainstay of chronic pain management and encompasses several modalities, including strength training, manual therapy, and massage.

Physical therapy can be beneficial for a variety of types of chronic pain. For musculoskeletal pain, hot or cold packs, massage, and stretching (including traction) can be helpful.

But physical therapy can help not just musculoskeletal pain but also neuropathic pain. For example, if there is a cervical radiculopathy, the position and posture of individual neck muscles may exacerbate the narrowing of the neuroforamina; or nerves may become entrapped within hypertrophied muscles, leading to neuropathic pain. Therefore, functional rehabilitation through physical therapy may address multiple types of pain.

Physical therapy for management of low-back pain may involve "core stabilization." Bounded by the diaphragm and the pelvic floor, the body's "core" is composed of the abdominal muscles and back and gluteal muscles. Exercises can help stabilize the entirety of the core, so that the low back does not need to exert as much effort for movement, lifting, bending, etc. "Core stabilization" can thereby decrease low-back pain.

Because physical therapy has minimal potential harms associated with it, as opposed to pharmacologic or interventional approaches for pain management, it should be a key component in management of both acute and chronic pain. While physical therapy can be used on its own, it is often preferable to engage in it as part of a multidisciplinary approach to pain management (which may include psychological therapies).

Araujo FM et al. Physical therapy modalities for treating fibromyalgia. F1000Res. 2019;8:F1000. [PMID: 32047594]
Martin-Gomez et al. Motor control using cranio-cervical flexion exercises versus other treatments for non-specific chronic neck pain: a systematic review and meta-analysis. Musculoskelet Sci Pract. 2019;42:52. [PMID: 31030111]
Owen PJ et al. Which specific modes of exercise training are most effective for treating low back pain? Network meta-analysis. Br J Sports Med. 2020;54:1279. [PMID: 31666220]

Integrative Medicine Therapy

Integrative medicine therapies of acupuncture, chiropractic care, biofeedback, meditation, music therapy, guided imagery, cognitive distraction, and framing may be helpful in treating pain.

SELECTED INTERVENTIONAL MODALITIES FOR PAIN RELIEF

Pain management specialists are physicians who have completed a residency in anesthesiology, physical medicine and rehabilitation, neurology, internal medicine, emergency medicine, or psychiatry and usually also a fellowship in pain management to learn medication management and interventional techniques for acute, chronic, and cancer pain. Interventional pain management modalities performed by pain management specialists involve neuromodulation of specific targets to alleviate pain. The procedures they perform include percutaneous needle injection of local anesthetics or corticosteroids, radiofrequency (thermal) lesioning, cryotherapy, chemical neurolysis, or surgical implantation of intrathecal medication delivery pump systems or neurostimulation devices. While invasive procedures carry their own inherent risks such as bleeding or infection, they can drastically reduce or even obviate the need for conventional pharmacologic therapies that may have side effects or be burdensome to the individual.

For some patients, a nerve block, such as a celiac plexus block for pain from pancreatic cancer, can provide substantial relief. Intrathecal pumps may be most useful for patients with severe pain responsive to opioids but who require such large doses that systemic side effects (eg, sedation, urinary retention, and constipation) become limiting. In the palliative care setting, these pumps are appropriate when life expectancy is long enough to justify the discomfort and cost of surgical implantation.

Clinicians do not need to know all the details of interventional pain procedures but should consider referring their patients to pain management specialists if such procedures may be beneficial. For example, a common question is whether prolonged opioid therapy with its inherent risks is better than an injection or an implanted device. Beyond knowing the benefits and risks, fiscal considerations may be key.

Tables 5–12 and 5–13 list the procedures and the agents typically used in interventional pain modalities.

Table 5–12. Interventional techniques for chronic pain by anatomic location.

Neuraxial
Intrathecal
Epidural (caudal, lumbar, thoracic, cervical; interlaminar vs transforaminal)
Paraneuraxial (planar blockade)
Paravertebral (intercostal)
Transversus abdominis plane/quadratus lumborum
Pectoralis and serratus anterior
Peripheral nerve (perineural blockade)
Brachial plexus and branches
Lumbar plexus and branches
Joints
Intra-articular injections
Joint denervation procedures
Sympathetic ganglion
Gasserian ganglion
Sphenopalatine ganglion
Cervical sympathetic blockade (stellate ganglion)
Lumbar sympathetic blockade
Celiac plexus
Superior hypogastric plexus
Ganglion impar
Continuous neuraxial drug delivery
Epidural (tunneled catheter, port)
Intrathecal (implanted intrathecal pump)
Neurostimulation
Dorsal column stimulation (spinal cord stimulation)
Dorsal root ganglion stimulation
Peripheral nerve or field stimulation

INTRATHECAL DRUG DELIVERY SYSTEM

A. Indications

Intrathecal drug delivery therapy is indicated for patients with both malignant and nonmalignant pain and has been shown to be effective, cost-effective, and safe. It is generally accepted that intrathecal opioids have a 100- to 300-fold efficacy compared with oral opioids; therefore, the best candidates may be patients with good analgesic benefit from opioids but burdensome side effects. Common indications include cancer pain, chronic low-back pain (in particular, post-laminectomy syndrome), complex regional pain syndrome, and other causes of neuropathic pain. In a randomized controlled trial comparing intrathecal therapy with comprehensive medication management in cancer pain, intrathecal therapy was shown to be superior in analgesia and fewer side effects. Due to the cost of implanting the device as well as the recovery time needed from surgical implantation, it is recommended that patients have a life expectancy of at least 2–3 months.

Table 5–13. Agents used[1] in neuromodulatory therapies.

Voltage-gated sodium channel blockade—local anesthetics
Lidocaine
Mepivacaine
Bupivacaine
Ropivacaine
Corticosteroids
Triamcinolone
Methylprednisolone
Dexamethasone
Opioids
Morphine
Hydromorphone
Fentanyl
Adjuvants
Clonidine
Dexmedetomidine
Others
Chemical neurolysis
Alcohol
Phenol
Glycerol
Thermal neurolysis
Radiofrequency ablation
Cryoanalgesia
Neurostimulation
Various patterns, frequency, amplitude, pulse width

[1]Injected or applied.
List is not comprehensive but includes most commonly used agents.

B. Procedure

Intrathecal drug delivery systems consist of a pump with a drug reservoir, typically implanted in the abdominal wall, connected to a catheter that delivers medications into the intrathecal space. Initial percutaneous trialing is indicated for patients with noncancer or cancer pain; such percutaneous trialing may consist of either epidural or intrathecal delivery of bolus or continuous medication to determine efficacy and side effect profiles of planned therapeutic agent(s). Some cancer patients may not undergo a trial to avoid delaying final implantation. Subsequent implantation of an intrathecal drug delivery system involves two incisions: one in the spine to accommodate the catheter and anchor, and another in the lower abdominal region to create a pocket to hold the pump. The catheter is tunneled through the lower abdominal and flank subcutaneous tissues to connect to the pump. Both trial and implantation are typically performed under sedation with local anesthetic infiltration; spinal anesthesia delivered from the pump itself can also be utilized for pump implantation. Some patients may require general anesthesia to tolerate the implantation procedure.

C. Medications Used

According to the Polyanalgesic Consensus Conference (PACC) guidelines for both malignant and nonmalignant pain, first-line intrathecal delivery medications include monotherapy with either morphine or ziconotide, a calcium channel inhibitor. However, the PACC guidelines also state that de facto practice includes combination therapy with opioids (eg, fentanyl, hydromorphone) and local anesthetic (eg, bupivacaine) and may include other medications (eg, baclofen or clonidine). Respiratory depression and sedation are two of the most concerning side effects of many intrathecal medications. Ziconotide may cause myositis and polyarthralgias as well as psychiatric and neurologic adverse effects (it is contraindicated in patients with preexisting psychosis). Side effects of morphine and fentanyl include nausea, edema, constipation, urinary retention, and pruritus.

D. Advantages and Disadvantages

The main advantage of intrathecal delivery therapy is targeted delivery of medication to the spinal cord with increased efficacy and diminished side effects compared with systemic analgesic medications. Intrathecal therapy has been found to be effective with decreased side effects and improved analgesia in 80% of cancer patients. The increased efficacy is due to the 100- to 300-fold increased concentration of intrathecal drug compared with systemic medication. However, intrathecal therapy requires regular pump refills and may be complicated by infections, catheter or pump malfunctions requiring surgical revision, or development of catheter tip granulomas, potentially leading to inadequate analgesia or neurologic deficits. Pump batteries may last from 5 years to 10 years depending on usage. Fatalities surrounding intrathecal therapy have been linked to respiratory depression; patients must be monitored for respiratory depression or sedation when initiating or increasing intrathecal therapeutic agents. Some intrathecal pumps need to be emptied prior to MRI; due to the magnetic forces of the MRI, the entirety of the drug reservoir could inadvertently open. Therefore, it is critical that the type of pump is known prior to placing the patient and pump in an MRI machine. Additionally, anticoagulants and NSAIDs need to be stopped prior to pump implantation and need to be held briefly after the implantation as well; this temporary cessation imposes the risk of potentially causing blood clots.

E. Alternatives

For patients with limited life expectancy, continuous epidural drug delivery via an external pump or subcutaneous port may be more appropriate. Systemic medication delivered orally, intravenously, topically, or even by a subcutaneous infusion (as in palliative care settings) are alternatives to intrathecal therapy.

Abd-Elsayed A et al. Intrathecal drug delivery for chronic pain syndromes: a review of considerations in practice management. Pain Physician. 2020;23:E591. [PMID: 33185379]
Sindt JE et al. Initiation of intrathecal drug delivery dramatically reduces systemic opioid use in patients with advanced cancer. Neuromodulation. 2020;23:978. [PMID: 32459393]

Sindt JE et al. The rate of infectious complications after intrathecal drug delivery system implant for cancer-related pain is low despite frequent concurrent anticancer treatment or leukopenia. Anesth Analg. 2020;131:280. [PMID: 31990731]
Sommer B et al. Long-term outcome and adverse events of intrathecal opioid therapy for nonmalignant pain syndrome. Pain Pract. 2020;20:8. [PMID: 31291509]
Spiegel MA et al. Evaluation of an intrathecal drug delivery protocol leads to rapid reduction of systemic opioids in the oncological population. J Palliat Med. 2021;24:418. [PMID: 32640912]

SPINAL STIMULATION

A. Indications

Spinal stimulation targets neuropathic pain in the trunk and limbs, such as failed back surgery syndrome, complex regional pain syndrome, and radiculopathy. There is also growing literature around its use for neuropathic pain associated with cancer.

B. Procedure

Neurostimulation devices consist of an implantable pulse generator typically placed in the flank or abdomen just under the skin and an array of electrical contacts on small cylindrical or paddle leads placed in the epidural space. **Neurostimulation** devices transmit electrical pulses to the spinal cord or dorsal root ganglion to block pain transmission. Paddle leads require neurosurgical implantation with laminotomy (and general anesthesia), while percutaneous wire leads may be implanted under sedation. Patients undergo a 3- to 7-day trial during which the leads are attached to an external battery source and undergo programming with different pulse waveforms to assess therapeutic efficacy prior to surgical implantation of permanent leads and implantable pulse generator.

C. Frequencies Used

Traditional neurostimulation resulted in paresthesias that were used to mask pain. It was presumed that these paresthesias were the result of stimulation of the dorsal column axons. Recent studies have revealed that analgesia can be obtained independent of paresthesias by altering a variety of spinal cord stimulation parameters, including constant high-frequency stimulation and burst high-frequency stimulation. More recent double-blind, randomized, controlled trials have revealed that both functional status and pain scores could be significantly improved in spinal cord stimulation systems that were capable of adapting the output to the patient's individual neural response in a closed loop fashion. For more focal neuropathic pain conditions such as postoperative inguinal nerve injuries or thoracic post herpetic neuralgias, stimulation of the dorsal root ganglion is able to provide focal analgesia. These newer, more versatile systems deliver paresthesia-free analgesia with analgesic response rates that have steadily increased from about 50% with the traditional devices to about 80%. The newer devices also have greater longevity and most are MRI compatible.

D. Advantages and Disadvantages

Spinal cord stimulation is a reversible technology that may provide superior analgesic efficacy while eliminating the need for systemic medications. Current literature suggests spinal cord stimulation is efficacious in 80–90% of well-selected patients, such as those with neuropathic low-back pain due to post-laminectomy syndrome. In fact, spinal cord stimulation has now advanced to a higher position in the treatment continuum; it can be considered before using long-term moderate doses of systemic opioids. On the other hand, because it is a surgical procedure, it may be associated with complications, such as infection, lead migration, device malfunction, or neurologic deficits. While MRIs were contraindicated with some older systems, most newer systems allow for limited MRI imaging. Batteries may require daily charging but typically do not require replacement for 5–10 years. Similar to intrathecal pumps, anticoagulants and NSAIDs need to be stopped prior to implantation of spinal cord stimulation devices because of the potential risks (eg, bleeding). The implanting surgeon, prescribing physician, and patient need to discuss the benefits and risks before proceeding.

E. Alternatives

In addition to medication management for pain, two neuromodulatory techniques may serve as alternatives to dorsal horn and dorsal root ganglion stimulation. Peripheral nerve stimulation is an emerging technology; it targets peripheral nerves using a similar system of a lead connected to a pulse generator. It may be most appropriate when there is a very specific neurologic target. Transcutaneous electrical nerve stimulators (TENS) and systemic pharmacologic therapies are alternatives.

Deer TR et al. A systematic literature review of spine neurostimulation therapies for the treatment of pain. Pain Med. 2020;21:1421. [PMID: 32034422]
Hofmeister M et al. Effectiveness of neurostimulation technologies for the management of chronic pain: a systematic review. Neuromodulation. 2020;23:150. [PMID: 31310417]
Mekhail N et al. Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. Lancet Neurol. 2020;19:123. [PMID: 31870766]
Mekhail N et al. Choice of spinal cord stimulation versus targeted drug delivery in the management of chronic pain: a predictive formula for outcomes. Reg Anesth Pain Med. 2020;45:131. [PMID: 31932490]
Moisset X et al. Neurostimulation methods in the treatment of chronic pain. J Neural Transm (Vienna). 2020;127:673. [PMID: 31637517]

CELIAC PLEXUS BLOCK & NEUROLYSIS

A. Indications

A celiac plexus block refers to injection of a long-acting anesthetic (eg, bupivacaine) with or without a corticosteroid (eg, methylprednisolone); with steroids, the block can

provide relief for a few weeks to months. Celiac plexus neurolysis involves injection of a neurolytic agent (eg, alcohol or phenol); it may provide pain relief more consistently for 2–6 months. The most common indication is pancreatic cancer pain, but it can be used for pain from other malignancies (eg, stomach, liver, spleen, kidney, and GI tract) or from chronic pancreatitis. Multiple randomized controlled trials and meta-analyses have shown superiority of celiac plexus neurolysis to medication management for pancreatic cancer, but evidence of its efficacy for chronic pancreatitis is more mixed.

B. Procedure

The most common approach is a percutaneous posterior approach under fluoroscopy guidance, with bilateral needles targeted to the celiac plexus at the level of T12–L1. Alternatively, ultrasound, CT, or endoscopic guidance can be used. Minimal sedation is required for the percutaneous approaches, while heavy sedation or general anesthesia may be required for endoscopic guidance.

C. Medications Used

Chemical neurolysis with alcohol or phenol is used to extend the duration of the analgesia to 2 or more months compared to a block with local anesthetic (eg, bupivacaine) and corticosteroid (eg, methylprednisolone), which produces an analgesic duration of weeks to months. For chemical neurolysis, alcohol is used most often because it does not require compounding, and importantly has a lower chance of permanent neurologic damage compared with phenol; however, it is more painful on injection.

D. Advantages and Disadvantages

The primary advantage is improved analgesia without need for systemic medications and their untoward effects. Neurolytic celiac plexus blockade is effective in 70–80% of patients. Common side effects of celiac plexus interventions include transient hypotension and transient diarrhea. Transient or permanent spinal cord damage is rare, although there is an increased risk of its occurrence with plexus (chemical) neurolysis compared with plexus (anesthetic) block.

E. Alternatives

Standard pain management is with oral or transdermal systemic analgesic (eg, opioid) medication. Intrathecal therapy is also an alternative, especially for cancer pain.

Filippiadis DK et al. Percutaneous neurolysis for pain management in oncological patients. Cardiovasc Intervent Radiol. 2019;42:791. [PMID: 30783779]

Lau J et al. Interventional anesthesia and palliative care collaboration to manage cancer pain: a narrative review. Can J Anaesth. 2020;67:235. [PMID: 31571119]

Urits I et al. A comprehensive review of the celiac plexus block for the management of chronic abdominal pain. Curr Pain Headache Rep. 2020;24:42. [PMID: 32529305]

EPIDURAL CORTICOSTEROID INJECTION

A. Indications

Epidural corticosteroid injections are indicated for patients with chronic neck pain, low-back pain, and radicular pain resulting from central or neuroforaminal stenosis in the cervical, thoracic, or lumbosacral region. Both central and neuroforaminal stenosis may be caused by degenerative disk disease, disk herniation, or facet arthropathy. Epidural corticosteroid injections are relatively safe and are appropriate after conservative measures, such as physical therapy and analgesic medications, have been tried and found unsuccessful.

B. Procedure

Fluoroscopy is typically used to assist with visualizing the bony landmarks; either an interlaminar or a transforaminal approach can be used. Interlaminar access is obtained by placing a needle between the lamina of adjacent vertebral levels, whereas transforaminal access is obtained by inserting a needle through the neuroforamen to access the epidural space. These needle insertion procedures can be performed with topical local anesthetic or with minimal sedation.

C. Medications Used

Typically, a particulate corticosteroid such as methylprednisolone is used alone or in combination with a local anesthetic. For the transforaminal approach, where vascular access is more of a concern, a nonparticulate corticosteroid such as dexamethasone may be preferred.

D. Advantages and Disadvantages

Epidural corticosteroid injections are advantageous for patients who have not responded to conservative therapy, are not surgical candidates, or do not want surgery. The best evidence of the effectiveness of epidural corticosteroid injections is the short-term improvement of radiculopathy in both the lumbar and cervical regions. In a Cochrane analysis, side effects were noted in 10–24% of surgical cases but no side effects were reported for any conservative treatments. Disadvantages include possible postdural puncture headache, transient weakness, and, rarely, permanent neurologic deficits. Patients who are receiving systemic anticoagulation may need to hold their anticoagulants before receiving corticosteroid injections, which could increase their risk of cardiovascular events; these cases should be discussed with the clinician managing the anticoagulation prior to performing any epidural corticosteroid injections.

E. Alternatives

Alternatives include conservative therapy, such as oral analgesic medication management, physical therapy, pain psychology, acupuncture, and surgery.

Verheijen EJA et al. Epidural steroid compared to placebo injection in sciatica: a systematic review and meta-analysis. Eur Spine J. 2021;30:3255. [PMID: 33974132]
Yang S et al. Epidural steroid injection versus conservative treatment for patients with lumbosacral radicular pain. Medicine (Baltimore). 2020;99:e21283. [PMID: 32791709]

When to Refer

Patients should be referred to pain management specialists if they have:

- Pain that does not respond to opioids at typical doses or the opioids cause major adverse effects at typical doses.
- Pain that cannot be controlled expeditiously or safely by other clinicians.
- Neuropathic pain that does not respond to first-line treatments.
- Complex medication management that uses buprenorphine or methadone.
- Severe pain from malignancy, including primary disease (eg, pancreatic cancer) or metastatic disease (eg, bony metastases).

When to Admit

- Severe exacerbation of pain not responsive to previous stable oral opioids given around-the-clock plus breakthrough doses.
- Pain that is so severe that it cannot be controlled at home.
- Uncontrollable side effects from opioids, including nausea, vomiting, myoclonus, and altered mental status.
- Need for a surgical procedure, such as implantation of an intrathecal drug delivery pump or neurostimulation device.

Dermatologic Disorders

6

Kanade Shinkai, MD, PhD
Lindy P. Fox, MD

Dermatologic diseases are diagnosed by the types of lesions they cause. Identify the morphology of lesion(s) to establish a differential diagnosis (Table 6–1), and obtain the elements of the history, physical examination, and appropriate laboratory tests to confirm the diagnosis. Specific clinical situations, such as an immunocompromised or critically ill patient, lead to different diagnostic considerations.

PRINCIPLES OF DERMATOLOGIC THERAPY

Frequently Used Treatment Measures

A. Bathing

Soap should be used only in the axillae and groin and on the feet by persons with dry or inflamed skin. Soaking in water for 10–15 minutes before applying topical corticosteroids or emollient enhances their efficacy (Soak and Smear).

B. Topical Therapy

Nondermatologists should become familiar with a representative agent in each category for each indication (eg, topical corticosteroid, topical retinoid, etc).

1. Corticosteroids—Topical corticosteroid creams, lotions, ointments, gels, foams, and sprays are presented in Table 6–2. Topical corticosteroids are divided into classes based on potency. Agents within the same class are equivalent therapies; however, prices of topical corticosteroids vary dramatically. For a given agent, higher lipophilicity (greasiness) corresponds with increased potency; ie, triamcinolone 0.1% ointment is more potent than triamcinolone 0.1% cream which in turn is more potent than triamcinolone 0.1% lotion. The potency of a topical corticosteroid may be dramatically increased by occlusion (covering with a water-impermeable barrier) for at least 4 hours. Depending on the location of the skin condition, gloves, plastic wrap, moist pajamas covered by dry pajamas (wet wraps), or plastic occlusive suits for patients can be used. Caution should be used in applying topical corticosteroids to areas of thin skin (face, genitals, skin folds). Topical corticosteroid use on the eyelids may result in glaucoma or cataracts. One may estimate the amount of topical corticosteroid needed by using the "rule of nines" (as in burn evaluation; see Figure 37–2). Approximately 20–30 g is needed to cover the entire body surface of an adult. Systemic absorption does occur with topical corticosteroids, but complications of systemic corticosteroids are rare.

2. Emollients for dry skin ("moisturizers")—Dry skin is a result of abnormal function of the epidermis. Emollients restore the epidermis by promoting keratinocyte differentiation and by producing innate antimicrobials; some restore skin barrier lipids, including ceramides. Ointments and creams, rather than lotion, are the best moisturizers. **Emollients are most effective when applied to wet skin.** If the skin is too greasy after application, pat dry with a damp towel. Plain petrolatum is allergen-free and can be used if allergic contact dermatitis to topical products is suspected.

The scaly appearance of dry skin may be improved by emollients with concomitant use of keratolytics including urea, lactic acid, or glycolic acid–containing products provided no inflammation (erythema or pruritus) is present.

3. Drying agents for weepy dermatoses—If the skin is weepy from infection or inflammation, drying agents may be beneficial. The best drying agent is water, applied as repeated compresses for 15–30 minutes, alone or with aluminum salts (Burow solution, Domeboro tablets).

4. Topical antipruritics—Lotions that contain 0.5% each of camphor and menthol (Sarna) or pramoxine hydrochloride 1% (with or without 0.5% menthol, eg, Prax, PrameGel, Aveeno Anti-Itch lotion) are effective antipruritic agents. Hydrocortisone, 1% or 2.5%, may be incorporated for its anti-inflammatory effect (Pramosone cream, lotion, or ointment). Doxepin cream 5% reduces pruritus but may cause drowsiness. Pramoxine and doxepin are most effective when applied with topical corticosteroids. Topical capsaicin and lidocaine can be effective in some forms of neuropathic itch.

C. Systemic Antipruritic Drugs

1. Antihistamines and antidepressants—H_1-blockers are the agents of choice for pruritus due to histamine, such as urticaria. Otherwise, they appear to benefit itchy patients

Table 6–1. Morphologic categorization of skin lesions and diseases.

Pigmented	Freckle, lentigo, seborrheic keratosis, nevus, blue nevus, halo nevus, atypical nevus, melanoma, actinic keratoses, Bowen disease, Paget disease
Scaly	Psoriasis, dermatitis (atopic, stasis, seborrheic, chronic allergic contact or irritant contact), xerosis (dry skin), lichen simplex chronicus, tinea pedis/cruris/corporis, tinea versicolor, secondary syphilis, pityriasis rosea, discoid lupus erythematosus, exfoliative dermatitis, drug eruption
Vesicular	Herpes simplex, varicella, herpes zoster, pompholyx (vesicular dermatitis of palms and soles), vesicular tinea, autoeczematization, dermatitis herpetiformis, miliaria crystallina, scabies, photosensitivity, acute contact allergic dermatitis, drug eruption
Weepy or encrusted	Impetigo, acute contact allergic dermatitis, any vesicular dermatitis
Pustular	Acne vulgaris, acne rosacea, folliculitis, candidiasis, miliaria pustulosa, pustular psoriasis, any vesicular dermatitis, drug eruption
Figurate ("shaped") erythema	Urticaria, erythema multiforme, erythema migrans, cellulitis, erysipelas, erysipeloid, arthropod bites
Bullous	Impetigo, blistering dactylitis, pemphigus, pemphigoid, porphyria cutanea tarda, drug eruptions, erythema multiforme, toxic epidermal necrolysis
Papular	**Hyperkeratotic:** warts, corns, seborrheic keratoses **Purple-violet:** lichen planus, drug eruptions, Kaposi sarcoma, lymphoma cutis, Sweet syndrome **Flesh-colored, umbilicated:** molluscum contagiosum **Pearly:** basal cell carcinoma, intradermal nevi **Small, red, inflammatory:** acne, rosacea, miliaria rubra, candidiasis, scabies, folliculitis
Pruritus[1]	Xerosis, scabies, pediculosis, lichen planus, lichen simplex chronicus, bites, systemic causes, anogenital pruritus
Nodular, cystic	Erythema nodosum, furuncle, cystic acne, follicular (epidermal) inclusion cyst, metastatic tumor to skin
Photodermatitis	Drug eruption, polymorphic light eruption, lupus erythematosus
Morbilliform	Drug eruption, viral infection, secondary syphilis
Erosive	Any vesicular dermatitis, impetigo, aphthae, lichen planus, erythema multiforme, intertrigo
Ulcerated	Decubiti, herpes simplex, skin cancers, parasitic infections, syphilis (chancre), chancroid, vasculitis, stasis, arterial disease, pyoderma gangrenosum

[1]Not a morphologic class but included because it is one of the most common dermatologic presentations.

Table 6–2. Useful topical dermatologic therapeutic agents.[1]

Agent	Formulations, Strengths, and Prices[2]	Frequency of Application	Potency Class	Common Indications	Comments
Corticosteroids (Listed in Order of Increasing Potency)					
Hydrocortisone acetate	Cream 1%: $3.99/30 g Ointment 1%: $1.58/28 g Solution 1%: $7.34/44 mL	Twice daily	Low	Seborrheic dermatitis Pruritus ani Intertrigo	Not the same as valerate or hydrocortisone butyrate Not for poison oak OTC lotion (Aquanil HC), OTC solution (Scalpicin)
	Cream 2.5%: $9.66/28 g Ointment 2.5%: $11.00/28 g			As for 1% hydrocortisone	Perhaps better for pruritus ani Not clearly better than 1% More expensive Not OTC
Alclometasone dipropionate (Aclovate)	Cream 0.05%: $48.08/15 g Ointment 0.05%: $20.00/15 g	Twice daily	Low	As for hydrocortisone	More efficacious than hydrocortisone Perhaps causes less atrophy
Desonide	Cream 0.05%: $21.60/15 g Ointment 0.05%: $23.21/15 g Lotion 0.05%: $296.09/59 mL	Twice daily	Low	As for hydrocortisone For lesions on face or body folds resistant to hydrocortisone	More efficacious than hydrocortisone Can cause rosacea or atrophy Not fluorinated

(*continued*)

Table 6–2. Useful topical dermatologic therapeutic agents.[1] (continued)

Agent	Formulations, Strengths, and Prices[2]	Frequency of Application	Potency Class	Common Indications	Comments
Clocortolone (Cloderm)	Cream 0.1%: $322.47/45 g	Three times daily	Medium	Contact dermatitis Atopic dermatitis	Does not cross-react with other corticosteroids chemically and can be used in patients allergic to other corticosteroids
Prednicarbate (Dermatop)	Emollient cream 0.1%: $137.10/60 g Ointment 0.1%: $30.00/15 g	Twice daily	Medium	As for triamcinolone	May cause less atrophy No generic formulations Preservative-free
Triamcinolone acetonide	Cream 0.1%: $3.60/15 g Ointment 0.1%: $5.57/15 g Lotion 0.1%: $42.42/60 mL	Twice daily	Medium	Eczema on extensor areas Used for psoriasis with tar Seborrheic dermatitis and psoriasis on scalp	Caution in body folds, face Economical in 0.5-lb and 1-lb sizes for treatment of large body surfaces Economical as solution for scalp
	Cream 0.025%: $4.50/15 g Ointment 0.025%: $10.11/80 g	Twice daily	Medium	As for 0.1% strength	Possibly less efficacy and few advantages over 0.1% formulation
Fluocinolone acetonide	Cream 0.025%: $44.85/15 g Ointment 0.025%: $33.77/15 g	Twice daily	Medium	As for triamcinolone	
	Solution 0.01%: $90.00/60 mL	Twice daily	Medium	As for triamcinolone	
Mometasone furoate (Elocon)	Cream 0.1%: $29.16/15 g Ointment 0.1%: $25.92/15 g Lotion 0.1%: $57.04/60 mL	Once daily	Medium	As for triamcinolone	Often used inappropriately on the face or on children Not fluorinated
Desoximetasone	Cream 0.05%: $62.43/15 g Cream 0.25%: $40.00/15 g Gel 0.05%: $298.38/60 g Ointment 0.25%: $18.00/15 g	Twice daily	High	As for triamcinolone	Comparable potency to fluocinonide Suggested for use when allergic contact dermatitis to topical corticosteroid is suspected; ointment useful when allergic contact dermatitis to propylene glycol is suspected
Diflorasone diacetate	Cream 0.05%: $209.68/15 g Ointment 0.05%: $209.68/15 g	Twice daily	High	Nummular dermatitis Allergic contact dermatitis Lichen simplex chronicus	
Fluocinonide (Lidex)	Cream 0.05%: $45.55/15 g Gel 0.05%: $59.56/15 g Ointment 0.05%: $70.75/15 g Solution 0.05%: $84.00/60 mL	Twice daily	High	As for betamethasone Gel useful for poison oak	Economical generics Lidex cream can cause stinging on eczema Lidex emollient cream preferred
Betamethasone dipropionate (Diprolene)	Cream 0.05%: $44.00/15 g Ointment 0.05%: $50.45/15 g Lotion 0.05%: $43.19/60 mL	Twice daily	Ultra-high	For lesions resistant to high-potency corticosteroids Lichen planus Insect bites	Economical generics available

(*continued*)

Table 6–2. Useful topical dermatologic therapeutic agents.[1] (continued)

Agent	Formulations, Strengths, and Prices[2]	Frequency of Application	Potency Class	Common Indications	Comments
Clobetasol propionate (Temovate)	Cream 0.05%: $127.10/15 g Ointment 0.05%: $149.23/15 g Lotion 0.05%: $288.96/59 mL	Twice daily	Ultra-high	As for betamethasone dipropionate	Somewhat more potent than diflorasone Limited to 2 continuous weeks of use Limited to 50 g or less per week Cream may cause stinging; use "emollient cream" formulation Generic available
Halobetasol propionate (Ultravate)	Cream 0.05%: $39.60/15 g Ointment 0.05%: $75.58/15 g	Twice daily	Ultra-high	As for clobetasol	Same restrictions as clobetasol Cream does not cause stinging Compatible with calcipotriene (Dovonex)
Flurandrenolide (Cordran)	Tape: $857.28/24″ × 3″ roll Lotion 0.05%: $360.00/120 mL	Every 12 hours	Ultra-high	Lichen simplex chronicus	Tape version protects the skin and prevents scratching
Nonsteroidal Anti-inflammatory Agents (Listed Alphabetically)					
Crisaborole (Eucrisa)	Ointment 2%: $830.35/60 g	Twice daily	N/A	Atopic dermatitis	Steroid substitute not causing atrophy or striae May sting or burn on initial application
Pimecrolimus[3] (Elidel)	Cream 1%: $608.71/60 g	Twice daily	N/A	Atopic dermatitis	Steroid substitute not causing atrophy or striae
Tacrolimus[3] (Protopic)	Ointment 0.1%: $240.00/60 g Ointment 0.03%: $168.01/60 g	Twice daily	N/A	Atopic dermatitis	Steroid substitute not causing atrophy or striae Burns in ≥ 40% of patients with eczema May cause flushing with ingestion of alcohol
Antibiotics (for Acne) (Listed Alphabetically)					
Clindamycin phosphate	Solution 1%: $28.94/30 mL Gel 1%: $54.00/30 mL Lotion 1%: $115.38/60 mL Pledget 1%: $50.58/60	Twice daily	N/A	Mild papular acne	Lotion is less drying than solution, gel, or pledgets for patients with sensitive skin Recommend use with benzoyl peroxide to avoid antibiotic resistance from monotherapy
Clindamycin/Benzoyl peroxide (BenzaClin)	Gel: $90.00/25 g Gel: $180.00/50 g	Twice daily	N/A	As for benzamycin	No generic More effective than either agent alone
Dapsone	Gel 5%: $601.27/60 g	Once daily	N/A	Mild papulopustular acne	More expensive, well tolerated Recommend use with benzoyl peroxide to avoid antibiotic resistance from monotherapy

(*continued*)

Table 6–2. Useful topical dermatologic therapeutic agents.[1] (continued)

Agent	Formulations, Strengths, and Prices[2]	Frequency of Application	Potency Class	Common Indications	Comments
Erythromycin	Solution 2%: $47.63/60 mL Gel 2%: $60.48/30 g Pledget 2%: $92.65/60	Twice daily	N/A	As for clindamycin	Many different manufacturers Economical Recommend use with benzoyl peroxide to avoid antibiotic resistance from monotherapy
Erythromycin/ Benzoyl peroxide (Benzamycin)	Gel: $199.08/23.3 g Gel: $75.00/46.6 g	Twice daily	N/A	As for clindamycin Can help treat comedonal acne	No generic More expensive More effective than other topical antibiotics Main jar requires refrigeration
Minocycline	Foam: 4% $582.00/30 g	Once daily	N/A	As for clindamycin	No generic More expensive May cause skin yellowing (temporary, washes off)
Antibiotics (for Impetigo)					
Mupirocin (Bactroban)	Ointment 2%: $11.25/22 g Cream 2%: $245.16/15 g	Three times daily	N/A	Impetigo, folliculitis	Because of cost, use limited to tiny areas of impetigo Used in the nose twice daily for 5 days to reduce staphylococcal carriage
Retapamulin (Altabax)	Ointment 1%: $401.05/15 g	Twice daily	N/A	Impetigo	For *Staphylococcus aureus* or *Streptococcus pyogenes* infection Typically reserved for mupirocin-resistant infections
Ozenoxacin (Ozanex)	Cream 1%: $374.22/30 g	Twice daily (5 days)	N/A	Impetigo	Topical fluoroquinolone Activity against MRSA
Antifungals: Imidazoles (Listed Alphabetically)					
Clotrimazole	Cream 1%: $2.99/15 g OTC Solution 1%: $33.68/10 mL	Twice daily	N/A	Dermatophyte and *Candida* infections	Available OTC Inexpensive generic cream available
Econazole (Spectazole)	Cream 1%: $30.04/15 g	Once daily	N/A	As for clotrimazole	Somewhat more effective than clotrimazole and miconazole
Ketoconazole (Nizoral)	Cream 2%: $30.90/15 g	Once daily	N/A	As for clotrimazole	Somewhat more effective than clotrimazole and miconazole
Miconazole	Cream 2%: $2.99/28 g OTC	Twice daily	N/A	As for clotrimazole	As for clotrimazole
Oxiconazole (Oxistat)	Cream 1%: $614.73/30 g Lotion 1%: $771.91/30 mL	Twice daily	N/A	As for clotrimazole	
Sertaconazole (Ertaczo)	Cream 2%: $1079.41/60 g	Twice daily	N/A	Refractory tinea pedis	By prescription More expensive
Sulconazole (Exelderm)	Cream 1%: $72.38/15 g Solution 1%: $416.66/30 mL	Twice daily	N/A	As for clotrimazole	No generic Somewhat more effective than clotrimazole and miconazole

(*continued*)

Table 6–2. Useful topical dermatologic therapeutic agents.[1] (continued)

Agent	Formulations, Strengths, and Prices[2]	Frequency of Application	Potency Class	Common Indications	Comments
Other Antifungals (Listed Alphabetically)					
Butenafine (Mentax)	Cream 1%: $8.01/12 g OTC	Once daily	N/A	Dermatophytes	Fast response; high cure rate; expensive Available OTC
Ciclopirox (Loprox) (Penlac)	Cream 0.77%: $51.10/30 g Lotion 0.77%: $80.75/30 g Solution 8%: $60.18/6.6 mL	Twice daily	N/A	As for clotrimazole	No generic Somewhat more effective than clotrimazole and miconazole
Efinaconazole (Jublia)	Solution 10%: $818.69/4 mL	Once daily for 48 weeks	N/A	Onychomycosis	No generic; more effective than ciclopirox for nail disease
Naftifine (Naftin)	Cream 1%: $375.38/60 g Gel 1%: $522.38/60 mL	Once daily	N/A	Dermatophytes	No generic Somewhat more effective than clotrimazole and miconazole
Tavaborole (Kerydin)	Solution 5%: $616.42/4 mL	Once daily for 48 weeks	N/A	Onychomycosis	No generic available
Terbinafine (Lamisil)	Cream 1%: $8.72/12 g OTC	Once daily	N/A	Dermatophytes	Fast clinical response OTC
Antipruritics (Listed Alphabetically)					
Camphor/menthol (Sarna)	Lotion 0.5%/0.5%: $8.96/222 mL	Two to three times daily	N/A	Mild eczema, xerosis, mild contact dermatitis	
Capsaicin (various)	Cream 0.025%: $9.95/60 g Cream 0.075%: $10.39/56 g	Three to four times daily	N/A	Topical antipruritic, best used for neuropathic itching	Burning/stinging with initial application that subsides with consistent ongoing use
Doxepin (Zonalon)	Cream 5%: $802.56/45 g	Four times daily	N/A	Topical antipruritic, best used in combination with appropriate topical corticosteroid to enhance efficacy	Can cause sedation
Pramoxine hydrochloride (Prax)	Lotion 1%: $19.64/120 mL OTC	Four times daily	N/A	Dry skin, varicella, mild eczema, pruritus ani	OTC formulations (Prax, Aveeno Anti-Itch Cream or Lotion; Itch-X Gel) By prescription mixed with 1% or 2% hydrocortisone

[1]For a given agent, higher lipophilicity (greasiness) corresponds with increased potency; for example, triamcinolone 0.1% ointment is more potent than triamcinolone 0.1% cream, which in turn is more potent than triamcinolone 0.1% lotion.
[2]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions. IBM Micromedex ®Red Book (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www-micromedexsolutions-com.proxy.hsl.ucdenver.edu/ (cited March 15, 2022).
[3]Topical tacrolimus and pimecrolimus should be used only when other topical treatments are ineffective. Treatment should be limited to an area and duration be as brief as possible. Use of these agents should be avoided in persons with known immunosuppression, HIV infection, bone marrow and organ transplantation, or lymphoma; those at high risk for lymphoma; and those with a history of lymphoma.
MRSA, methicillin-resistant *Staphylococcus aureus;* N/A, not applicable; OTC, over-the-counter.

only by their sedating effects. Hydroxyzine 25–50 mg orally at night is a typical dose. Sedating and nonsedating antihistamines are of limited value for the treatment of pruritus associated with inflammatory skin disease. Preferable agents include antidepressants (such as doxepin, mirtazapine, and paroxetine) and agents that act directly on the neurons that perceive or modulate pruritus (such as gabapentin, pregabalin, and duloxetine).

2. Systemic corticosteroids—(See Chapter 26.)

Andrade A et al. Interventions for chronic pruritus of unknown origin. Cochrane Database Syst Rev. 2020;1:CD013128. [PMID: 31981369]
Axon E et al. Safety of topical corticosteroids in atopic eczema: an umbrella review. BMJ Open. 2021;11:e046476. [PMID: 34233978]
Stacey SK et al. Topical corticosteroids: choice and application. Am Fam Physician. 2021;103:337. [PMID: 33719380]

Sunscreens

Protection from UV light reduces the incidence of sunburn, actinic keratoses, melanoma, and some nonmelanoma skin cancers when initiated at any age and in any skin type. The best protection is shade, but protective clothing, avoidance of direct sun exposure during the peak hours of the day, and daily use of sunscreens are important.

A broad-spectrum (protection against UVA and UVB) sunscreen should be used daily with a sun protective factor (SPF) of at least 30. Clinicians should reinforce regular sunscreen use and reapplication every few hours or more depending on exercise level and exposure to water. Health implications of systemic absorption of chemical sunscreens are unknown.

Lyons AB et al. Photoprotection beyond ultraviolet radiation: a review of tinted sunscreens. J Am Acad Dermatol. 2021;84:1393. [PMID: 32335182]
Matta MK et al. Effect of sunscreen application on plasma concentration of sunscreen active ingredients: a randomized clinical trial. JAMA. 2020;323:256. [PMID: 31961417]

Complications of Topical Dermatologic Therapy

Complications of topical therapy include allergy, irritation, and other side effects. Reactions may result from the active or inactive ingredients, including fragrances and preservatives.

A. Allergy

Of the topical antibiotics, neomycin and bacitracin have the greatest potential for sensitization. Diphenhydramine, benzocaine, vitamin E, aromatic oils, preservatives, fragrances, tea tree oil, and even topical corticosteroids can cause allergic contact dermatitis.

B. Irritation

Preparations of tretinoin, benzoyl peroxide, and other acne medications should be applied sparingly to the skin.

C. Other Side Effects

Topical corticosteroids may induce acne-like lesions on the face (steroid rosacea) and atrophic striae in body folds.

deGroot A. Allergic contact dermatitis from topical drugs: an overview. Dermatitis. 2021;32:197. [PMID: 34415695]

NEOPLASTIC LESIONS

PIGMENTED NEOPLASMS

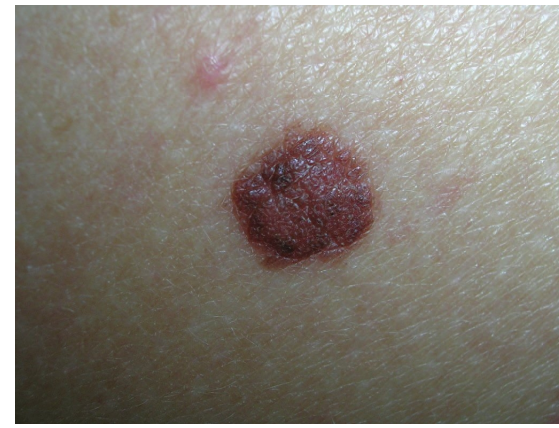
BENIGN PIGMENTED LESIONS

1. Melanocytic Nevi (Normal Moles)

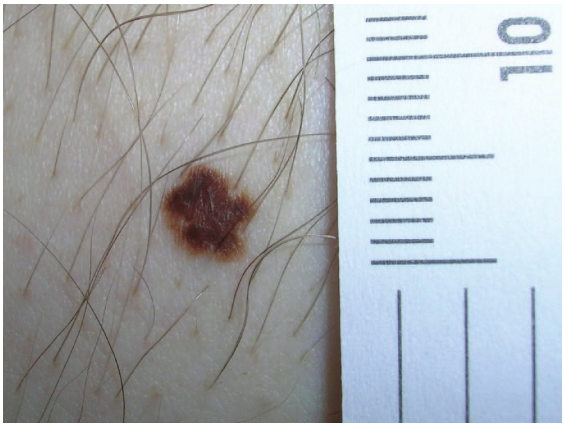
In general, a benign mole is a small (less than 6 mm) macule or papule with a well-defined border and homogeneous beige or pink to dark brown pigment. They represent benign melanocytic growths.

Moles have a typical natural history. Early in life, moles often appear as flat, small, brown lesions and are termed "junctional nevi" because the nevus cells are at the junction of the epidermis and dermis. Over time, these moles enlarge and often become raised, reflecting the appearance of a dermal component, giving rise to "compound nevi" (Figure 6–1). Moles may darken and grow during pregnancy. As White patients enter their eighth decade, most moles have lost their junctional component and dark pigmentation as a result of normal senescence. At every stage of life, normal moles should be well demarcated, symmetric, and uniform in contour and color. Regular mole screening is not an evidence-based recommendation for all adults, although rates of screening continue to rise.

Ko E et al. Pigmented lesions. Dermatol Clin. 2020;38:485. [PMID: 32892857]
Yeh I. New and evolving concepts of melanocytic nevi and melanocytomas. Mod Pathol. 2020;33:1. [PMID: 31659277]



▲ **Figure 6–1.** Benign, compound nevus on the back. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)



▲ **Figure 6–2.** Atypical (dysplastic) nevus on the chest. Note irregular border and variegation in color. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

2. Atypical Nevi

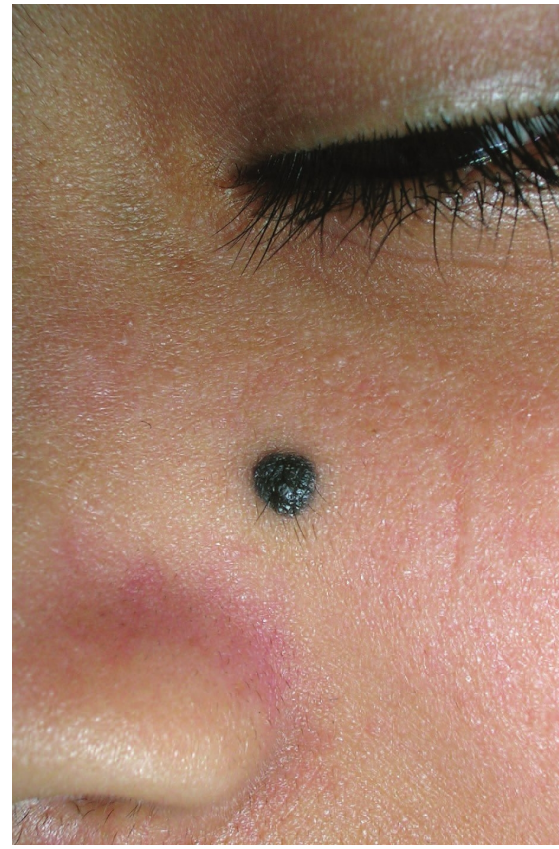
The term "atypical nevus" or "atypical mole" has supplanted "dysplastic nevus." The diagnosis of atypical moles is made clinically, not histologically. Moles should be removed only if they are suspected to be melanomas. Dermoscopy by a trained clinician may be a useful tool in the evaluation of atypical nevi. Clinically, these moles are large (6 mm or more in diameter), with an ill-defined, irregular border and irregularly distributed pigmentation (Figure 6–2). An estimated 5–10% of the White population in the United States has one or more atypical nevi, for which recreational sun exposure is a primary risk. There is an increased risk of melanoma in patients with 50 or more nevi with one or more atypical moles and one mole 8 mm or larger and patients with any number of definitely atypical moles. These patients should be educated in how to recognize changes in moles and be monitored every 6–12 months by a clinician. Kindreds with familial melanoma (numerous atypical nevi and a family history of two first-degree relatives with melanoma) require closer attention since their risk of developing single or multiple melanomas approaches 50% by age 50.

Elder DE et al. The 2018 World Health Organization Classification of cutaneous, mucosal, and uveal melanoma: detailed analysis of 9 distinct subtypes defined by their evolutionary pathway. Arch Pathol Lab Med. 2020;144:500. [PMID: 32057276]

Fried L et al. Technological advances for the detection of melanoma: advances in diagnostic techniques. J Am Acad Dermatol. 2020;83:983. [PMID: 32348823]

3. Blue Nevi

Blue nevi are small, slightly elevated, blue-black lesions (Figure 6–3) that favor the dorsal hands. They are common in persons of Asian descent and may be single or multiple. If the lesion has remained unchanged for years, it may be considered benign, since malignant blue nevi are rare.

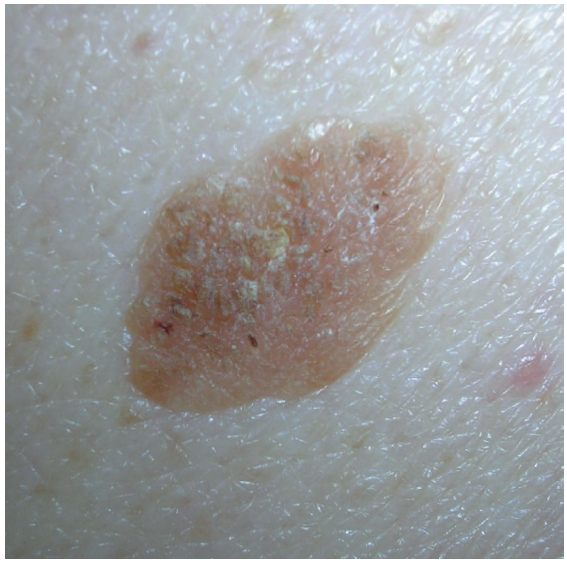


▲ **Figure 6–3.** Blue nevus on the left cheek, a darkly pigmented blue-black macule with some resemblance to a melanoma due to its dark pigmentation. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H, Tysinger J. *The Color Atlas of Family Medicine*. McGraw-Hill, 2009.)

Blue-black papules and nodules that are new or growing must be evaluated to rule out nodular melanoma.

4. Freckles & Lentigines

Freckles (ephelides) and lentigines are flat brown macules, typically between 3 mm and 5 mm in diameter. Freckles first appear in young children, darken with UV exposure, and fade with cessation of sun exposure. They are determined by genetic factors. In adults, lentigines gradually appear in sun-exposed areas, particularly the face, dorsal hands, upper back, and upper chest, starting in the fourth to fifth decade of life, and are associated with photoaging as well as estrogen and progesterone use. They may have a very irregular border (ink spot lentigines). They do not fade with cessation of sun exposure. They should be evaluated like all pigmented lesions: if the pigmentation is homogeneous and they are symmetric and flat, they are most likely benign. They can be treated with topical retinoids such as 0.1% tretinoin or 0.1% adapalene, hydroquinone, laser/light therapy, or cryotherapy.



▲ **Figure 6–4.** Seborrheic keratosis with light pigmentation, with waxy, dry, "stuck-on," appearance. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

5. Seborrheic Keratoses

Seborrheic keratoses are benign papules and plaques, beige to brown or even black, 3–20 mm in diameter, with a velvety or warty surface. They appear to be stuck or pasted onto the skin (Figure 6–4). They are extremely common—especially in older adults—and may be mistaken for melanomas or other types of cutaneous neoplasms. No treatment is needed. They may be frozen with liquid nitrogen or curetted if itchy or inflamed but usually recur after treatment.

Hruza GJ et al. Safety and efficacy of nanosecond pulsed electric field treatment of seborrheic keratoses. Dermatol Surg. 2020;46:1183. [PMID: 31809349]

MALIGNANT PIGMENTED LESIONS

1. Malignant Melanoma

ESSENTIALS OF DIAGNOSIS

- May be flat or raised with irregular borders.
- Examination may show varying colors, including red, white, black, and blue.
- Should be suspected in any pigmented skin lesion with recent change in appearance.
- Less than 30% develop from existing moles.

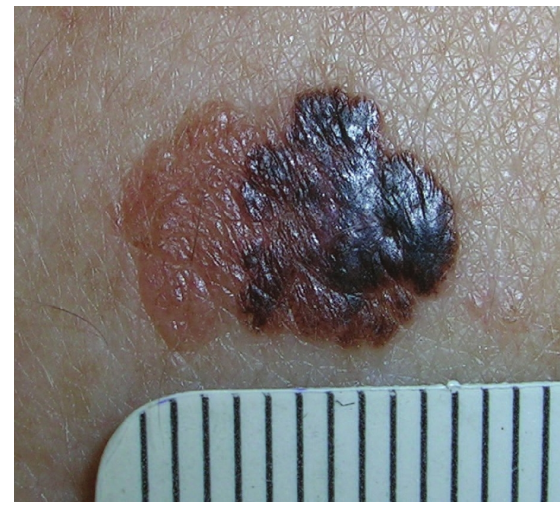
General Considerations

Malignant melanoma, the fifth most common of all cancers in the United States, is the leading cause of death due to skin disease and has doubled in incidence over the past 30 years. In 2021, approximately 106,110 new melanomas were diagnosed in the United States, with approximately 60% in men. In 2021, melanoma caused an estimated 7180 deaths (two-thirds in men). The lifetime risk of melanoma is 2% in White individuals and 0.1–0.5% in non-White persons. One in four cases occurs before age 40. Increased detection of early melanomas has led to increased survival, but fatalities continue to increase, especially in men older than 70 years.

Tumor thickness is the single most important prognostic factor. Ten-year survival rates related to melanoma thickness are less than 1 mm, 95%; 1–2 mm, 80%; and 2–4 mm, 55%. The 5-year survival rate is 62% with lymph node involvement and 16% with distant metastases.

Clinical Findings

Primary malignant melanomas may be classified into various clinicohistopathologic types, including lentigo melanoma (arising on chronically sun-exposed skin of older individuals); superficial spreading melanoma (two-thirds of all melanomas arising on intermittently sun-exposed skin); nodular melanoma; acral-lentiginous melanomas (arising on palms, soles, and nail beds); ocular melanoma; and melanomas on mucous membranes. Different types of melanoma appear to have distinct oncogenic mutations, which may be important in the treatment of patients with advanced disease. Less than 30% of melanomas develop from existing moles. Clinical features of pigmented lesions suspicious for melanoma are an irregular, notched border where the pigment appears to be spreading into the normal surrounding skin and irregular surface topography (ie, partly raised and partly flat) (Figure 6–5). Color variegation



▲ **Figure 6–5.** Malignant melanoma. Note the classic "ABCDE" features: asymmetry, irregular border, multiple colors, diameter greater than 6 mm, and evolution or change. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

is present and is an important indication for referral. A useful mnemonic is the ABCDE rule: Asymmetry, Border irregularity, Color variegation, Diameter greater than 6 mm, and Evolution. **The history of a changing mole (evolution, including bleeding and ulceration) is the single most important historical reason for close evaluation and possible referral.** A mole that appears distinct from the patient's other moles deserves special scrutiny—the "ugly duckling sign." A patient with a large number of moles is statistically at increased risk for melanoma and deserves annual total body skin examination by a primary care clinician or dermatologist, particularly if the lesions are atypical in appearance.

While superficial spreading melanoma is largely a disease of White individuals, persons with darker skin pigmentation are at risk for this and other types of melanoma, particularly acral lentiginous melanomas, for which UV exposure may not be a significant association. These occur as dark, irregularly shaped lesions on the palms and soles and as new, often broad and solitary, darkly pigmented, longitudinal streaks in the nails, typically with involvement of the proximal nail fold. Acral lentiginous melanoma may be a difficult or delayed diagnosis because benign pigmented lesions of the hands, feet, and nails occur commonly in more darkly pigmented persons, and clinicians may hesitate to biopsy these sites. Clinicians should give special attention to new or changing lesions in these areas.

Treatment

Treatment starts with complete excision of the melanoma with a normal margin. After histologic diagnosis, reexcision is recommended with margins dictated by the thickness of the tumor. Recommended surgical margins are 0.5–1 cm for melanoma in situ, 1 cm for lesions less than 1 mm in thickness, and 1–2 cm for lesions more than 1 mm in thickness.

Referral of intermediate-risk and high-risk patients to centers with expertise in melanoma is strongly recommended. Sentinel lymph node biopsy (selective lymphadenectomy) using preoperative lymphoscintigraphy and intraoperative lymphatic mapping is effective for staging melanoma patients with intermediate risk without clinical adenopathy and is recommended for all patients with lesions over 1 mm in thickness or with high-risk histologic features (ulceration). This procedure may not confer a survival advantage. Identifying the oncogenic mutations in patients with advanced melanoma may dictate targeted therapy, most commonly to specific BRAF mutations. Additionally, immunotherapy treatments directed toward immune costimulatory molecules such as PD-1 can activate systemic immune-directed destruction of metastatic melanoma.

Albittar AA et al. Immunotherapy for melanoma. Adv Exp Med Biol. 2020;1244:51. [PMID: 32301010]
Carr S et al. Epidemiology and risk factors of melanoma. Surg Clin North Am. 2020;100:1. [PMID: 31753105]
Swetter S et al. NCCN Guidelines® Insights: Melanoma: cutaneous, Version 2.2021. J Natl Compr Canc Netw. 2021;19:364. [PMID: 33845460]

NONPIGMENTED NEOPLASMS

BENIGN LESIONS

1. Epidermal Inclusion Cyst

ESSENTIALS OF DIAGNOSIS

- Firm dermal papule or nodule.
- Overlying black comedone or "punctum."
- Expressible foul-smelling cheesy material.
- May become red and drain, mimicking an abscess.

General Considerations

Epidermal inclusion cysts (EICs) are common, benign growths of the upper portion of the hair follicle. They are common in Gardner syndrome and may be the first sign of the condition.

EICs favor the face and trunk and may complicate nodulocystic acne vulgaris. Individual lesions range in size from 0.3 cm to several centimeters. An overlying pore or punctum is characteristic. Dermoscopy can aid in observing a tiny punctum when not visible to the naked eye. Lateral pressure may lead to extrusion of a foul-smelling, cheesy material.

Differential Diagnosis

EICs are distinguished from lipomas by being more superficial (in the dermis, not the subcutaneous fat) and by their overlying punctum. Many other benign and malignant tumors may superficially resemble EICs, but all lack the punctum.

Complications

EICs may rupture, creating an acute inflammatory nodule very similar to an abscess. Cultures of the expressed material will be sterile.

Treatment

Treatment is not required if asymptomatic. Small (1–3 cm) lesions can be treated with a punch incision and removal of cystic contents. Inflamed lesions may be treated with incision and drainage or intralesional triamcinolone acetomide 5–10 mg/mL. For large or symptomatic cysts, surgical excision is curative.

MALIGNANT & PREMALIGNANT LESIONS

1. Actinic Keratoses

Actinic keratoses are small (0.2–0.6 cm) papules—flesh-colored, pink, or slightly hyperpigmented—that feel like sandpaper and are tender to palpation. They occur on sun-exposed parts of the body in persons of fair complexion.

Actinic keratoses are considered premalignant; 1:1000 lesions per year progress to squamous cell carcinoma.

Application of liquid nitrogen provides rapid eradication of lesions, which crust and disappear in 10–14 days. "Field treatment" with a topical agent can be considered in patients with multiple lesions in one region (eg, forehead, dorsal hands, etc). Fluorouracil cream is the most effective topical agent used for field treatment; imiquimod, ingenol mebutate, and photodynamic therapy are also effective. Combination therapy may be clinically beneficial. Any lesions that persist should be evaluated for possible biopsy.

Cornejo CM et al. Field cancerization: treatment. J Am Acad Dermatol. 2020;83:719. [PMID: 32387663]
Dianzani C et al. Current therapies for actinic keratosis. Int J Dermatol. 2020;59:677. [PMID: 32012240]
Willenbrink TJ et al. Field cancerization: definition, epidemiology, risk factors, and outcomes. J Am Acad Dermatol. 2020;83:709. [PMID: 32387665]

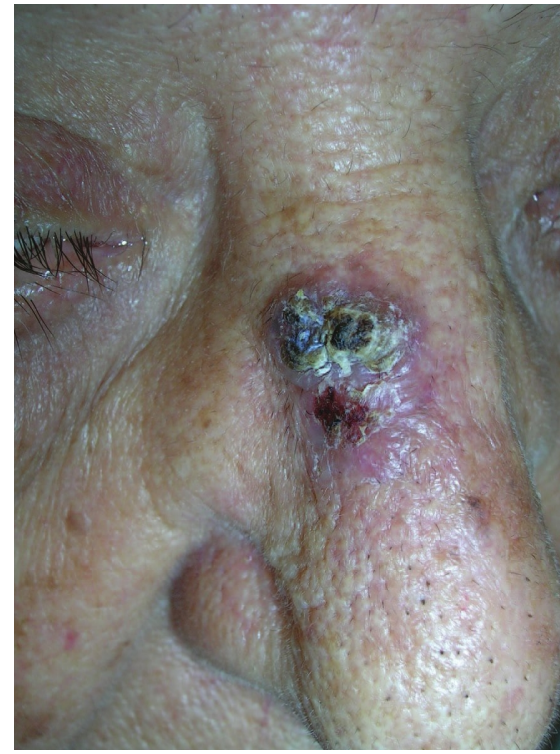
2. Squamous Cell Carcinoma

ESSENTIALS OF DIAGNOSIS

- Nonhealing ulcer or warty nodule.
- Skin damage due to long-term sun exposure.
- Common in fair-skinned organ transplant recipients.

Squamous cell carcinoma usually occurs subsequent to prolonged sun exposure on exposed parts in fair-skinned individuals who sunburn easily and tan poorly. It may arise from an actinic keratosis. The lesions appear as small red, conical, hard nodules that occasionally ulcerate (Figure 6–6). In actinically induced squamous cell cancers, rates of metastasis are estimated from retrospective studies to be 3–7%. Squamous cell carcinomas of the ear, temple, lip, oral cavity, tongue, and genitalia have much higher rates of recurrence or metastasis and require special management. Patients with multiple squamous cell carcinomas (especially more than 10) have higher rates of local recurrence and nodal metastases. Nicotinamide, 500 mg orally twice daily, can decrease the rate of development of squamous cell carcinomas by 30% in high-risk groups.

Squamous cell carcinoma in situ can be treated with imiquimod or 5-fluorouracil (in similar dosing as for superficial basal cell carcinoma) or curettage and electrodessication. The preferred treatment for invasive squamous cell carcinoma is excision or Mohs micrographic surgery. Mohs micrographic surgery is recommended for high-risk lesions (lips, temples, ears, nose), recurrent tumors, aggressive histologic subtypes (perineural or perivascular invasion), large lesions (greater than 1.0 cm on face, greater than 2.0 cm on trunk or extremities), immunosuppressed patients, lesions developing within a scar, and tumors arising in the setting of genetic diseases. Follow-up for squamous cell carcinoma must be more frequent and thorough than for basal cell carcinoma, starting at every 3 months, with careful examination of lymph nodes for 1 year, then twice yearly thereafter.



▲ **Figure 6–6.** Squamous cell carcinoma: an irregular-shaped pink plaque with overlying hemorrhagic crust in a chronically sun-exposed area. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Transplant patients with squamous cell carcinomas represent a highly specialized patient population. Biologic behavior of skin cancer in organ transplant recipients may be aggressive, and careful management is required. Multiple squamous cell carcinomas are very common on the sun-exposed skin of organ transplant patients. The tumors begin to appear after 5 years of immunosuppression. Regular dermatologic evaluation in at-risk organ transplant recipients is recommended. Other forms of immunosuppression, such as allogeneic hematopoietic stem cell transplants, chronic lymphocytic leukemia, HIV/AIDS, and chronic iatrogenic immunosuppression, may also increase skin cancer risk and be associated with more aggressive skin cancer behavior.

Cañueto J et al. Comparing the eighth and the seventh editions of the American Joint Committee on Cancer staging system and the Brigham and Women's Hospital alternative staging system for cutaneous squamous cell carcinoma: implications for clinical practice. J Am Acad Dermatol. 2019;80:106. [PMID: 30003984]
Firnhaber JM. Basal cell and cutaneous squamous cell carcinomas: diagnosis and treatment. Am Fam Physician. 2020;102:339. [PMID: 32931212]

3. Basal Cell Carcinoma

ESSENTIALS OF DIAGNOSIS

- Pearly papule, erythematous patch > 6 mm, or nonhealing ulcer in sun-exposed areas (face, trunk, lower legs).
- History of bleeding.
- Fair-skinned person with a history of sun exposure (often intense, intermittent).

General Considerations

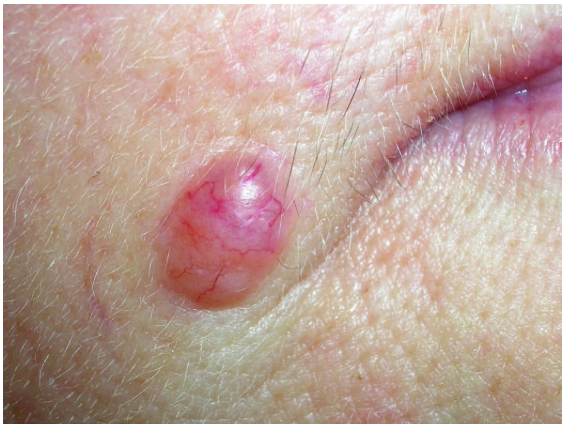
Basal cell carcinomas are the most common form of cancer. They occur on sun-exposed skin in otherwise normal, fair-skinned individuals; UV light is the cause. Basal cell carcinomas can be divided into clinical and histologic subtypes, which determine both clinical behavior and treatment. The clinical subtypes include superficial, nodular, pigmented, and morpheaform. The histologic subtypes include superficial, nodular, micronodular, and infiltrative. Morpheaform, micronodular, and infiltrative basal cell carcinomas are not amenable to topical therapy or electrodesiccation and curettage and typically require surgical excision or Mohs micrographic surgery. Because a second basal cell carcinoma develops in up to half of patients, skin examination is required at least yearly to detect new or recurrent lesions. Nicotinamide, 500 mg orally twice daily, can decrease the rate of development of basal cell carcinomas by 20% in high-risk groups.

Clinical Findings

The most common presentation is a papule or nodule that may have a central scab or erosion. Occasionally the nodules have stippled pigment (pigmented basal cell carcinoma). Intradermal nevi without pigment on the face of older White individuals may resemble basal cell carcinomas. Basal cell carcinomas grow slowly, attaining a size of 1–2 cm or more in diameter, usually only after years of growth. There is a waxy, "pearly" appearance, with telangiectatic vessels easily visible (Figure 6–7). It is the pearly or translucent quality of these lesions that is most diagnostic, a feature best appreciated if the skin is stretched. On the back and chest, basal cell carcinomas appear as reddish, somewhat shiny, scaly thin papules or plaques. Morpheaform basal cell carcinomas are scar-like in appearance. Basal cell carcinomas are more common and more likely to recur in immunosuppressed patients, including those with non-Hodgkin lymphoma and those who have undergone solid organ or allogeneic hematopoietic stem cell transplantation.

Treatment

Lesions suspected to be basal cell carcinomas should be biopsied by shave or punch biopsy. Therapy is then aimed at eradication with minimal cosmetic deformity. The histopathologic classification of basal cell carcinomas determines therapy. Imiquimod (applied topically 5 nights per week for 6–10 weeks depending on patient reaction) and 5-fluorouracil (applied topically twice daily for up to 12 weeks) may be appropriate for select patients with superficial basal cell carcinomas, but the treated area must be observed for evidence of complete cure. Superficial or nodular type lesions can be treated with curettage and electrodesiccation, excision, or Mohs micrographic surgery, while those that are classified as micronodular or infiltrative should be treated with excision or Mohs micrographic surgery depending on the size and location of the lesion.



▲ **Figure 6–7.** Pearly nodular basal cell carcinoma on the face of a 52-year-old woman present for 5 years. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Surgical excision has a recurrence rate of 5% or less. The technique of three cycles of curettage and electrodesiccation depends on the skill of the operator and is not recommended for head and neck lesions or basal cell carcinomas with morpheaform, infiltrative, or micronodular histopathology. After 4–6 weeks of healing, it leaves a broad, hypopigmented, at times hypertrophic scar.

Mohs micrographic surgery—removal of the tumor followed by immediate frozen section histopathologic examination of margins with subsequent reexcision of tumor-positive areas and final closure of the defect—gives the highest cure rates (98%) and results in least tissue loss. It is an appropriate therapy for tumors of the eyelids, nasolabial folds, canthi, external ear, and temple; for recurrent lesions; where tissue sparing is needed for cosmesis; and for those with morpheaform, infiltrative, or micronodular histopathology in certain locations.

Photodynamic therapy and topical application of a photosensitizing agent, followed by irradiation by a light source (typically blue or red), may be appropriate for some superficial and small nodular basal cell carcinomas.

Radiotherapy is effective and sometimes appropriate for older individuals (over age 65), but recurrent tumors after

radiation therapy are more difficult to treat and may be more aggressive. Radiation therapy is the most expensive method to treat basal cell carcinoma and should be used only if other treatment options are not appropriate.

Hedgehog pathway inhibitors (vismodegib, sonidegib) are reserved for the treatment of advanced or metastatic basal cell carcinoma or in patients with extensive tumor burden (eg, basal cell nevus syndrome).

Firnhaber JM. Basal cell and cutaneous squamous cell carcinomas: diagnosis and treatment. Am Fam Physician. 2020; 102:339. [PMID: 32931212]
Peris K et al; European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. Eur J Cancer. 2019;118:10. [PMID: 31288208]
Thomson J et al. Interventions for basal cell carcinoma of the skin. Cochrane Database Syst Rev. 2020;11:CD003412. [PMID: 33202063]

4. Kaposi Sarcoma

General Considerations

Human herpes virus 8 (HHV-8), or Kaposi sarcoma–associated herpes virus, is the cause of all forms of Kaposi sarcoma. Kaposi sarcoma occurs in five forms. **Classic Kaposi sarcoma** occurs in older men, has a chronic clinical course, and is rarely fatal. **Endemic Kaposi sarcoma** occurs in an often aggressive form in young Black men of equatorial Africa. **Iatrogenic Kaposi sarcoma** occurs in patients receiving immunosuppressive therapy and improves upon decreasing immunosuppression. **Epidemic Kaposi sarcoma** is associated with HIV-associated immune deficiency. A fifth type is an indolent form of **Kaposi sarcoma** that occurs exclusively in HIV-negative men who have sex with men.

Red or purple plaques or nodules on cutaneous or mucosal surfaces are characteristic. Marked edema may occur with few or no skin lesions. Kaposi sarcoma commonly involves the GI tract and can be screened for by fecal occult blood testing. In asymptomatic patients, these lesions are not sought or treated. Pulmonary Kaposi sarcoma can present with shortness of breath, cough, hemoptysis, or chest pain; it may be asymptomatic, appearing only on chest radiograph. Bronchoscopy may be indicated. The incidence of AIDS-associated Kaposi sarcoma is diminishing. However, chronic Kaposi sarcoma can develop in patients with HIV infection, high CD4 counts, and low viral loads. In this setting, the Kaposi sarcoma usually resembles the endemic form, being indolent and localized. At times, however, it can be clinically aggressive. The presence of Kaposi sarcoma at the time of antiretroviral initiation is associated with Kaposi sarcoma–immune reconstitution inflammatory syndrome, which has an especially aggressive course in patients with visceral disease.

Treatment

For Kaposi sarcoma in elders, palliative local therapy with intralesional chemotherapy or radiation is usually all that is required. In the setting of iatrogenic immunosuppression, the treatment of Kaposi sarcoma is primarily reduction of doses of immunosuppressive medications. In AIDS-associated Kaposi sarcoma, the patient should first be given ART. Other therapeutic options include cryotherapy or intralesional vinblastine (0.1–0.5 mg/mL) for cosmetically objectionable lesions; radiation therapy for accessible and space-occupying lesions; and laser surgery for certain intraoral and pharyngeal lesions. Systemic therapy is indicated in patients with skin disease that is cosmetically unacceptable or those with advanced cutaneous, oral visceral, or nodal disease. ART plus chemotherapy appears to be more effective than ART alone (see Table 39–3). First-line systemic therapies include liposomal doxorubicin and paclitaxel. Other therapeutic options include pomalidomide, etoposide, gemcitabine, imatinib, interferon alpha-2b, thalidomide, vinorelbine, bleomycin plus vincristine, bevacizumab, lenalidomide, and immune checkpoint inhibitors.

Dupin N. Update on oncogenesis and therapy for Kaposi sarcoma. Curr Opin Oncol. 2020;32:122. [PMID: 31815777]
Reid E et al. AIDS-Related Kaposi Sarcoma, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17:171. [PMID: 30787130]

5. Cutaneous T-Cell Lymphoma (Mycosis Fungoides)

ESSENTIALS OF DIAGNOSIS

- Localized or generalized erythematous patches that progress to scaly plaques and nodules.
- Sometimes associated with pruritus, lymphadenopathy.
- Distinctive histology.

General Considerations

Mycosis fungoides is a cutaneous T-cell lymphoma that begins on the skin and may remain there for years or decades. It may progress to systemic disease, including Sézary syndrome (erythroderma with circulating malignant T cells).

Clinical Findings

A. Symptoms and Signs

Localized or generalized erythematous patches or scaly plaques are present usually on the trunk. Plaques are almost always over 5 cm in diameter. Pruritus is a frequent complaint and can be severe. The lesions often begin as nondescript patches, and patients may have skin lesions for more than a decade before the diagnosis is confirmed. Follicular involvement with hair loss is characteristic of mycosis fungoides, and its presence should raise the suspicion of mycosis fungoides for any pruritic eruption. In more advanced cases, tumors appear. Local or diffuse

lymphadenopathy may be due to benign expansion (dermatopathic lymphadenopathy) or involvement with mycosis fungoides.

B. Laboratory Findings

Diagnosis is based on skin biopsy though numerous biopsies may be required before the diagnosis is confirmed. In more advanced disease, circulating malignant T cells (Sézary cells) can be detected in the blood (T-cell gene rearrangement test). Eosinophilia may be present.

Differential Diagnosis

Mycosis fungoides may be confused with psoriasis, drug eruption, photoallergy, eczematous dermatitis, syphilis, or tinea corporis. Histologic examination can distinguish these conditions.

Treatment

The treatment of mycosis fungoides is complex. Early and aggressive treatment has not been proven to cure or prevent disease progression. Skin-directed therapies, including topical corticosteroids, topical mechlorethamine, bexarotene gel, and UV phototherapy, are used initially. If the disease progresses, PUVA plus retinoids, PUVA plus interferon, extracorporeal photopheresis, bexarotene, histone deacetylase inhibitors (romidepsin or vorinostat), targeted immunomodulators (brentuximab, mogamulizumab), and total skin electron beam treatment are used.

Prognosis

Mycosis fungoides is usually slowly progressive (over decades). Prognosis is better with patch or plaque stage disease and worse with erythroderma, tumors, and lymphadenopathy. Survival is not reduced in patients with limited patch disease. Elderly patients with limited disease commonly die of other causes. Overly aggressive treatment may lead to complications and premature demise.

Kempf W et al. Cutaneous T-cell lymphomas—an update 2021. Hematol Oncol. 2021;39:46. [PMID: 34105822]
Zinzani P et al. Critical concepts and management recommendations for cutaneous T-cell lymphoma: a consensus-based position paper from the Italian Group of Cutaneous Lymphoma. Hematol Oncol. 2021;39:275. [PMID: 33855728]

6. Bowen Disease & Paget Disease

Bowen disease (intraepidermal squamous cell carcinoma) can develop on sun-exposed and non–sun-exposed skin. The lesion is usually a small (0.5–3 cm), well-demarcated, slightly raised, pink to red, scaly plaque and may resemble psoriasis or a large actinic keratosis. Lesions may progress to invasive squamous cell carcinoma. Excision or other definitive treatment such as topical treatment (fluorouracil or imiquimod) or photodynamic therapy is indicated.

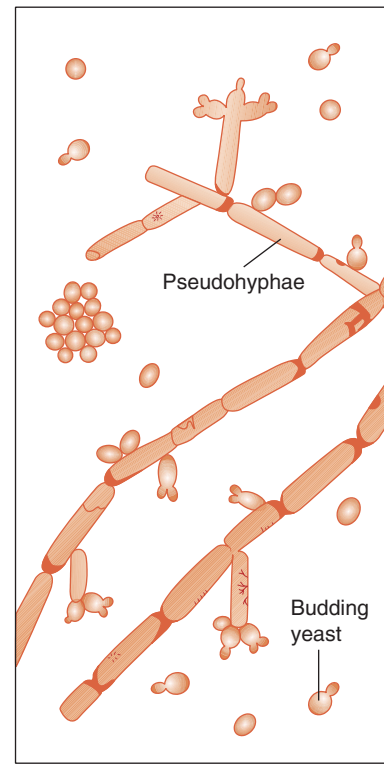
Extramammary Paget disease, a manifestation of intraepidermal carcinoma or underlying genitourinary or GI cancer, resembles chronic eczema and usually involves apocrine areas such as the genitalia. Mammary Paget disease of the nipple, a unilateral or rarely bilateral red scaling plaque that may ooze, is associated with an underlying intraductal mammary carcinoma (see Figure 17–3). While these lesions appear as red patches and plaques in fair-skinned persons, in darker-skinned individuals, hyperpigmentation may be prominent.

Morris CR et al. Extramammary Paget's disease: a review of the literature part ii: treatment and prognosis. Dermatol Surg. 2020;46:305. [PMID: 31688232]
Shim PJ et al. Photodynamic therapy for extramammary Paget's disease: a systematic review of the literature. Photodiagnosis Photodyn Ther. 2020;31:101911. [PMID: 32645437]

CUTANEOUS INFECTIONS, INFESTATIONS, & BITES

FUNGAL INFECTIONS

The diagnosis of fungal infections of the skin is based on the location and characteristics of the lesions and on the following laboratory examinations: (1) Direct demonstration of fungi in 10% KOH evaluation of suspected lesions. **"If it's scaly, scrape it" is a time-honored maxim** (Figure 6–8). (2) Cultures of organisms from skin scrapings. (3) Histologic sections of biopsies stained with periodic acid-Schiff technique may be diagnostic if scrapings and cultures are falsely negative.



▲ **Figure 6–8.** KOH preparation of fungus demonstrating pseudohyphae and budding yeast forms. (Reproduced, with permission, from Nicoll D et al. *Guide to Diagnostic Tests*, 7th ed. McGraw-Hill, 2017.)

Principles of Treatment

A diagnosis should always be confirmed by KOH preparation, culture, or biopsy. Many other diseases cause scaling, and use of an antifungal agent without a firm diagnosis makes subsequent diagnosis more difficult. In general, fungal infections are treated topically except for those with extensive involvement or involving the nails or hair follicles. In these situations, oral agents may be useful, with special attention to their side effects and complications, including hepatic toxicity.

General Measures & Prevention

Since moist skin favors the growth of fungi, dry the skin carefully after perspiring heavily or after bathing. The use of a hair dryer on a low setting may be helpful. Antifungal or drying powders may be useful with the exception of powders containing corn starch, which may exacerbate fungal infections. The use of topical corticosteroids for other diseases may be complicated by intercurrent tinea or candidal infection, and topical antifungals are often used in intertriginous areas with corticosteroids to prevent this.

TINEA CORPORIS OR TINEA CIRCINATA

ESSENTIALS OF DIAGNOSIS

- Ring-shaped lesions with an advancing scaly border and central clearing or scaly patches with a distinct border.
- Microscopic examination of scrapings or culture confirms the diagnosis.

General Considerations

The lesions are often on exposed areas of the body such as the face and arms. A history of exposure to an infected pet (who may have scaly rash or patches of alopecia) may occasionally be obtained, usually indicating *Microsporum* infection. *Trichophyton rubrum* is the most common pathogen, usually representing extension onto the trunk or extremities of tinea cruris, pedis, or manuum.

Clinical Findings

A. Symptoms and Signs

Itching may be present. In classic lesions, rings of erythema have an advancing scaly border and central clearing.

B. Laboratory Findings

The diagnosis should be confirmed by KOH preparation or culture.

Differential Diagnosis

Positive fungal studies distinguish tinea corporis from other skin lesions with annular configuration, such as the annular lesions of psoriasis, lupus erythematosus, syphilis, granuloma annulare, and pityriasis rosea. Psoriasis has typical lesions on elbows, knees, scalp, and nails. Secondary syphilis is often manifested by characteristic palmar, plantar, and mucous membrane lesions. Tinea corporis rarely has the large number of symmetric lesions seen in pityriasis rosea. Granuloma annulare lacks scale.

Complications

Complications include extension of the disease down the hair follicles (which presents as papules and pustules and requires systemic antifungals to cure) and pyoderma.

Prevention

Treat infected household pets (*Microsporum* infections). To prevent recurrences, the use of foot powder and keeping feet dry by wearing sandals or changing socks can be useful.

Treatment

A. Local Measures

Tinea corporis responds to most topical antifungals, including terbinafine, butenafine, econazole, miconazole, and clotrimazole, most of which are available over the counter in the United States (see Table 6–2). Terbinafine and butenafine require shorter courses and lead to the most rapid response. **Treatment should be continued for 1–2 weeks after clinical clearing**. Betamethasone dipropionate with clotrimazole (Lotrisone) is not recommended. Long-term improper use may result in side effects from the high-potency corticosteroid component, especially in body folds.

B. Systemic Measures

Itraconazole as a single weeklong pulse of 200 mg orally daily is effective in tinea corporis. Terbinafine, 250 mg orally daily for 1 month, is an alternative.

Prognosis

Tinea corporis usually responds promptly to conservative topical therapy or to an oral agent within 4 weeks.

Preda-Naumescu A et al. Common cutaneous infections: patient presentation, clinical course, and treatment options. Med Clin North Am. 2021;105:783. [PMID: 34059250]

TINEA CRURIS (Jock Itch)

ESSENTIALS OF DIAGNOSIS

- Marked itching in intertriginous areas, usually sparing the scrotum.
- Peripherally spreading, sharply demarcated, centrally clearing erythematous lesions.
- May have associated tinea infection of feet or toenails.
- Laboratory examination with microscope or culture confirms diagnosis.

General Considerations

Tinea cruris lesions are confined to the groin and gluteal cleft. Intractable pruritus ani may occasionally be caused by a tinea infection.

Clinical Findings

A. Symptoms and Signs

Itching may be severe, or the rash may be asymptomatic. The lesions have sharp margins, cleared centers, and active, spreading scaly peripheries. Follicular pustules are sometimes encountered. The area may be hyperpigmented on resolution.

B. Laboratory Findings

Hyphae can be demonstrated microscopically in KOH preparations or skin biopsy. The organism may be cultured.

Differential Diagnosis

Tinea cruris must be distinguished from other lesions involving the intertriginous areas, such as candidiasis, seborrheic dermatitis, intertrigo, psoriasis of body folds ("inverse psoriasis"), and erythrasma (corynebacterial infection of intertriginous areas). Candidiasis is generally bright red and marked by satellite papules and pustules outside of the main border of the lesion. *Candida* typically involves the scrotum. Seborrheic dermatitis also often involves the face, sternum, axillae, and genitalia (but not the crural folds). Intertrigo tends to be less red, less scaly, and present in obese individuals in moist body folds with less extension onto the thigh. "Inverse psoriasis" is characterized by distinct plaques. Other areas of typical psoriatic involvement should be checked, and the KOH examination will be negative. Erythrasma is best diagnosed with Wood (UV) light—a brilliant coral-red fluorescence is seen.

Treatment

A. General Measures

Drying powder (eg, miconazole nitrate [Zeasorb-AF]) can be dusted into the involved area in patients with excessive perspiration or occlusion of skin due to obesity as a preventive measure but is less helpful for treatment.

B. Local Measures

Any of the topical antifungal preparations listed in Table 6–2 may be used. Terbinafine cream is curative in over 80% of cases after once-daily use for 7 days.

C. Systemic Measures

One week of either itraconazole, 200 mg orally daily, or terbinafine, 250 mg orally daily, can be effective.

Prognosis

Tinea cruris usually responds promptly to topical or systemic treatment but often recurs.

Preda-Naumescu A et al. Common cutaneous infections: patient presentation, clinical course, and treatment options. Med Clin North Am. 2021;105:783. [PMID: 34059250]

TINEA MANUUM & TINEA PEDIS (Tinea of Palms & Soles)

ESSENTIALS OF DIAGNOSIS

- Most often presents with asymptomatic scaling.
- May progress to fissuring or maceration in toe web spaces.
- May be a portal of entry for bacteria causing lower extremity cellulitis.
- Itching, burning, and stinging of interdigital web; scaling palms and soles; vesicles on soles in inflammatory cases.
- KOH preparation or fungal culture of skin scapings is usually positive.

General Considerations

Tinea of the hands and feet (athlete's foot) is a common acute or chronic dermatosis. Most infections are caused by *Trichophyton* species.

Clinical Findings

A. Symptoms and Signs

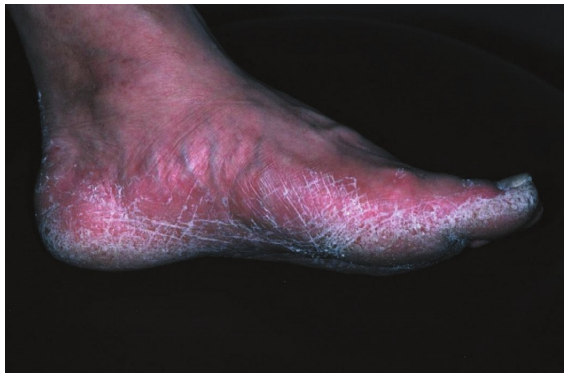
The presenting symptom may be itching, burning, or stinging. Pain may indicate secondary infection with complicating cellulitis. Interdigital tinea pedis is the most common predisposing cause of lower extremity cellulitis in healthy individuals. Regular examination of the feet of diabetic patients for evidence of scaling and fissuring and treatment of any identified tinea pedis may prevent complications. Tinea pedis has several presentations that vary with the location. On the sole and heel, tinea may appear as chronic noninflammatory scaling, occasionally with thickening and fissuring. This may extend over the sides of the feet in a "moccasin" distribution (Figure 6–9). The KOH preparation is usually positive. Tinea pedis often appears as a scaling or fissuring of the toe webs, often with maceration (Figure 6–10). As the web spaces become more macerated, the KOH preparation and fungal culture are less often positive because bacterial species begin to dominate. Finally, there may also be vesicles, bullae, or generalized exfoliation of the skin of the soles, or nail involvement in the form of discoloration, friability, and thickening of the nail plate.

B. Laboratory Findings

KOH and culture do not always demonstrate pathogenic fungi from macerated areas.

Differential Diagnosis

Another skin condition involving the same areas is interdigital erythrasma (use Wood light). Psoriasis may be a

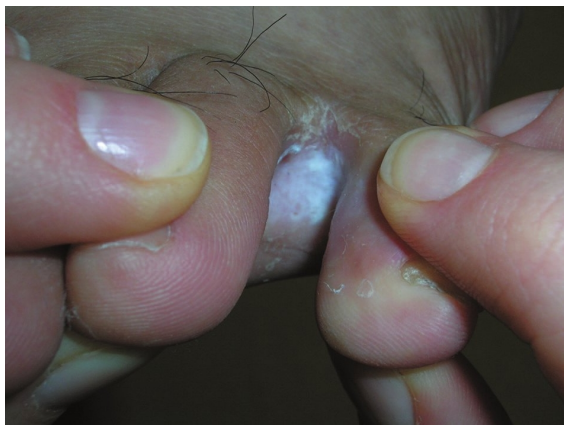


▲ **Figure 6–9.** Tinea pedis in the moccasin distribution. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

cause of chronic scaling on the palms or soles and may cause nail changes. Repeated fungal cultures should be negative, and the condition will not respond to antifungal therapy. Contact dermatitis will often involve the dorsal surfaces and will respond to topical or systemic corticosteroids. Vesicular lesions should be differentiated from pompholyx (dyshidrosis) and scabies by proper scraping of the roofs of individual vesicles. Rarely, gram-negative organisms may cause toe web infections, manifested as an acute erosive flare of interdigital disease. This entity is treated with aluminum salts and imidazole antifungal agents or ciclopirox. *Candida* may also cause erosive interdigital disease.

Prevention

The essential factor in prevention is personal hygiene. Wear open-toed sandals if possible. Use of sandals in community showers and bathing places is often recommended, though the effectiveness of this practice has not been studied. Careful drying between the toes after showering is essential. A hair dryer used on cooler setting may be helpful. Socks should be changed frequently, and absorbent nonsynthetic socks are preferred. Apply dusting and drying powders as necessary. The use of powders containing antifungal agents (eg, Zeasorb-AF) or long-term use of antifungal creams may prevent recurrences of tinea pedis.



▲ **Figure 6–10.** Tinea pedis in the interdigital space between fourth and fifth digits. The differential diagnosis includes a bacterial primary or secondary infection with gram-negative organisms. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

Treatment

A. Local Measures

1. Macerated stage—Treat with aluminum subacetate solution soaks for 20 minutes twice daily. Broad-spectrum antifungal creams and solutions (containing imidazoles or ciclopirox) (Table 6–2) will help combat diphtheroids and other gram-positive organisms present at this stage and alone may be adequate therapy. If topical imidazoles fail, 1 week of once-daily topical allylamine treatment (terbinafine or butenafine) will often result in clearing.

2. Dry and scaly stage—Use any of the antifungal agents listed in Table 6–2. The addition of urea 10–20% lotion or cream may increase the efficacy of topical treatments in thick ("moccasin") tinea of the soles.

B. Systemic Measures

Itraconazole, 200 mg orally daily for 2 weeks or 400 mg daily for 1 week, or terbinafine, 250 mg orally daily for 2–4 weeks, may be used in refractory cases. If the infection is cleared by systemic therapy, the patient should be encouraged to begin maintenance with topical therapy, since recurrence is common.

Prognosis

For many individuals, tinea pedis is a chronic affliction, temporarily cleared by therapy only to recur. Treatment of tinea pedis or manuum without systemic treatment of affected nails may result in recurrent skin disease.

Foley K et al. Topical and device-based treatments for fungal infections of the toenails. Cochrane Database Syst Rev. 2020;1:CD012093. [PMID: 31978269]

TINEA VERSICOLOR (Pityriasis Versicolor)

ESSENTIALS OF DIAGNOSIS

- Velvety, tan, pink, or white macules or white macules that do not tan with sun exposure.
- Fine scales that are not visible but are seen by scraping the lesion.
- Central upper trunk the most frequent site.
- Yeast and short hyphae observed on microscopic examination of scales.

General Considerations

Tinea versicolor is a mild, superficial *Malassezia* infection of the skin (usually of the upper trunk). This yeast is a colonizer of all humans, which accounts for the high recurrence rate after treatment. The eruption is often called to patients' attention by the fact that the involved areas will not tan, and the resulting hypopigmentation may be mistaken for vitiligo. A hyperpigmented form is not uncommon.

Clinical Findings

A. Symptoms and Signs

Lesions are asymptomatic, but a few patients note itching. The lesions are velvety, tan, pink, or white macules or thin papules that vary from 4 mm to 5 mm in diameter to large confluent areas. The lesions initially do not look scaly, but scales may be readily obtained by scraping the area. Lesions may appear on the trunk, upper arms, neck, and groin.

B. Laboratory Findings

Large, blunt hyphae and thick-walled budding spores ("spaghetti and meatballs") are seen on KOH. Fungal culture is not useful.

Differential Diagnosis

Vitiligo usually presents with larger periorificial and acral lesions and is also characterized by total (not partial) depigmentation. Vitiligo does not scale. Pink and red-brown lesions on the chest are differentiated from seborrheic dermatitis of the same areas by the KOH preparation.

Treatment & Prognosis

A. Initial Treatment

Topical treatments include selenium sulfide lotion, which may be applied from neck to waist daily and left on for 5–15 minutes for 7 days; this treatment is repeated weekly for a month. Ketoconazole shampoo, 1% or 2%, lathered on the chest and back and left on for 5 minutes may also be used weekly for treatment. Clinicians must stress to the patient that the raised and scaly aspects of the rash are being treated; the alterations in pigmentation may take months to fade or fill in.

A regimen of two doses of oral fluconazole, 300 mg, 14 days apart, is first-line treatment; the risk of hepatitis is minimal. Additional doses may be required in severe cases or humid climates. Ketoconazole is no longer recommended as first-line treatment because of the risk of drug-induced hepatitis.

B. Maintenance Therapy

Topical treatments as described above can be used for maintenance therapy. Selenium sulfide lotion should be used monthly, and ketoconazole shampoo, 1% or 2%, may be used to prevent recurrence. Imidazole creams, solutions, and lotions (eg, clotrimazole or miconazole) are quite effective for localized areas but are too expensive for use over large areas, such as the chest and back. Without maintenance therapy, recurrences will occur in over 80% of "cured" cases.

Bakr E et al. Adapalene gel 0.1% vs ketoconazole cream 2% and their combination in treatment of pityriasis versicolor: a randomized clinical study. Dermatol Ther. 2020;33:e13319. [PMID: 32182387]

MUCOCUTANEOUS CANDIDIASIS

ESSENTIALS OF DIAGNOSIS

- Severe pruritus of vulva, anus, or body folds.
- Superficial denuded, beefy-red areas with or without satellite vesicopustules.
- Whitish curd-like concretions on the oral and vaginal mucous membranes.
- Yeast and pseudohyphae on microscopic examination of scales or curd.

General Considerations

Mucocutaneous candidiasis is a superficial fungal infection that may involve almost any cutaneous or mucous surface. It is particularly likely to occur in diabetic patients, during pregnancy, in obese persons, and in the setting of immunosuppression. Systemic antibiotics, oral corticosteroids, hormone replacement therapy, and oral contraceptive agents may be contributory. Oral and interdigital candidiasis may be the first sign of HIV infection (see Chapter 31). Denture use predisposes the elderly to infection. Abnormalities in the IL-17, IL-22, mannose-binding lectin, and toll-like receptors have all been implicated in predisposing patients to *Candida* infection of the skin and mucous membranes.

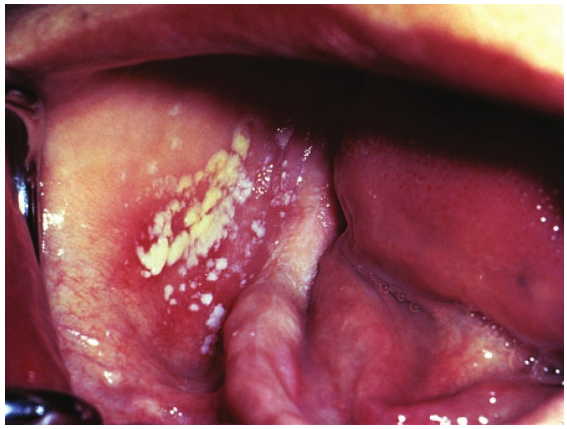
Clinical Findings

A. Symptoms and Signs

Itching may be intense. Burning is reported, particularly around the vulva and anus. The lesions consist of superficially denuded, beefy-red areas in the depths of the body folds, such as in the groin and the intergluteal cleft, beneath the breasts, at the angles of the mouth, in the webspaces of digits, and in the umbilicus. The peripheries of these denuded lesions are superficially undermined, and there may be satellite vesicopustules. Whitish, curd-like concretions may be present on mucosal lesions (Figure 6–11). Paronychia may occur.

B. Laboratory Findings

Clusters of budding yeast and pseudohyphae can be seen under high power (400×) when skin scales or curd-like



▲ **Figure 6–11.** Oral mucosal candidiasis. (Sol Silverman, Jr., D.D.S/Centers for Disease Control and Prevention.)

lesions are mounted in 10% KOH. Culture can confirm the diagnosis.

Differential Diagnosis

Intertrigo, seborrheic dermatitis, tinea cruris, "inverse psoriasis," and erythrasma involving the same areas may mimic mucocutaneous candidiasis.

Complications

Systemic invasive candidiasis with candidemia may occur in patients who are immunosuppressed or receiving broad-spectrum antibiotic or intravenous hypertonic glucose solutions (eg, hyperalimentation). There may or may not be clinically evident mucocutaneous candidiasis.

Treatment

A. General Measures

Affected parts should be kept dry and exposed to air as much as possible. Water immersion should be minimized and gloves should be worn for those with infected nails or digital skin. If possible, discontinue systemic antibiotics. For treatment of systemic invasive candidiasis, see Chapter 36.

B. Local Measures

1. Nails and paronychia—Apply clotrimazole solution 1% twice daily. Thymol 4% in ethanol applied once daily is an alternative.

2. Skin—Apply nystatin ointment or clotrimazole cream 1%, with hydrocortisone cream 1–2.5%, twice daily. Gentian violet 0.5% solution is economical and highly effective in treating mucocutaneous candidiasis, but the purple discoloration may represent a cosmetic issue. Severe or widespread cutaneous disease responds to fluconazole, 100–200 mg orally daily, for 1 week.

3. Vulvar and anal mucous membranes—For vaginal candidiasis, single-dose fluconazole (150 mg orally) is effective. Intravaginal clotrimazole, miconazole, terconazole, or nystatin may also be used. Long-term suppressive therapy may be required for recurrent or "intractable" cases. Non-albicans candidal species may be identified by culture in some refractory cases and may respond to oral itraconazole, 200 mg twice daily for 2–4 weeks.

4. Balanitis—This is most frequent in uncircumcised men, usually caused by *Candida*. Topical nystatin ointment is the initial treatment if the lesions are mildly erythematous or superficially erosive. Soaking with dilute 5% aluminum acetate for 15 minutes twice daily may quickly relieve burning or itching. Chronicity and relapses, especially after sexual contact, suggest reinfection from a sexual partner who should be treated. Severe purulent balanitis is usually due to bacteria. If it is so severe that phimosis occurs, oral antibiotics—some with activity against anaerobes—are required; if rapid improvement does not occur, urologic consultation is indicated.

5. Mastitis—Lancinating breast pain and nipple dermatitis in breast-feeding women may be a manifestation of *Candida* colonization/infection of the breast ducts. Topical nystatin cream and clotrimazole 0.1% cream are safe during lactation. Topical gentian violet 0.5% daily for 7 days is also useful. Oral fluconazole, 200 mg daily for 2 weeks, is effective and safe during lactation.

Prognosis

Cases of cutaneous candidiasis range from the easily cured to the intractable and prolonged.

Puel A. Human inborn errors of immunity underlying superficial or invasive candidiasis. Hum Genet. 2020;139:1011. [PMID: 32124012]

Yano J et al. Current patient perspectives of vulvovaginal candidiasis: incidence, symptoms, management and post-treatment outcomes. BMC Womens Health. 2019;19:48. [PMID: 30925872]

INTERTRIGO

Intertrigo is caused by the macerating effect of heat, moisture, and friction. It is especially likely to occur in obese persons and in humid climates. The symptoms are itching, stinging, and burning. The body folds develop fissures, erythema, maceration, and superficial denudation. Candidiasis may complicate intertrigo. "Inverse psoriasis," seborrheic dermatitis, tinea cruris, erythrasma, and candidiasis must be ruled out.

Maintain hygiene in the area and keep it dry. Compresses may be useful acutely. Hydrocortisone 1% cream plus an imidazole or clotrimazole 1% cream is effective. Recurrences are common.

Kottner J et al. Prevalence of intertrigo and associated factors: a secondary data analysis of four annual multicentre prevalence studies in the Netherlands. Int J Nurs Stud. 2020;104:103437. [PMID: 32105975]

VIRAL INFECTIONS

HERPES SIMPLEX (Cold or Fever Sore; Genital Herpes)

ESSENTIALS OF DIAGNOSIS

- Recurrent small grouped vesicles (especially orolabial and genital) on an erythematous base.
- May follow minor infections, trauma, stress, or sun exposure.
- Regional tender lymphadenopathy may occur.
- Direct fluorescent antibody tests are positive.

General Considerations

Over 85% of adults have serologic evidence of herpes simplex type 1 (HSV-1) infections, most often acquired asymptomatically in childhood. Occasionally, primary infections may be manifested as severe gingivostomatitis. Thereafter, the patient may have recurrent self-limited attacks, provoked by sun exposure, orofacial surgery, fever, viral infection, or immunosuppression.

About 25% of the US population has serologic evidence of infection with herpes simplex type 2 (HSV-2). HSV-2 causes lesions whose morphology and natural history are similar to those caused by HSV-1 but are typically located on the genitalia or buttocks of both sexes. The infection is acquired by sexual contact. In monogamous heterosexual couples where one partner has HSV-2 infection, seroconversion of the noninfected partner occurs in 10% over a 1-year period. Up to 70% of such infections appeared to be transmitted during periods of asymptomatic shedding. Genital herpes may also be due to HSV-1.

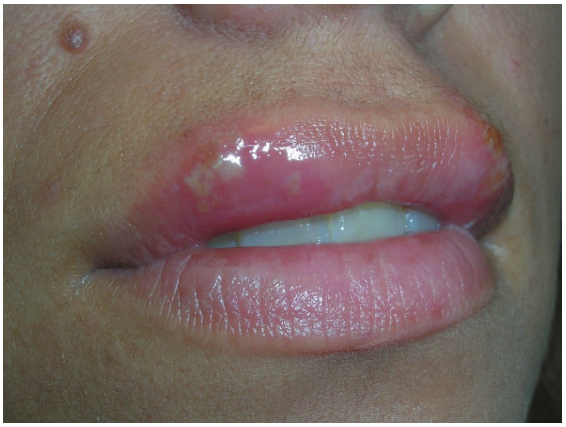
Clinical Findings

A. Symptoms and Signs

The principal symptoms are burning and stinging. Neuralgia may precede or accompany attacks. The lesions consist of small, grouped vesicles on an erythematous base that can occur anywhere but that most often occur on the vermilion border of the lips (Figure 6–12), the oral cavity, penile shaft, the labia, the perianal skin, and the buttocks. Any erosion or fissure in the anogenital region can be due to herpes simplex. Regional lymph nodes may be swollen and tender. The lesions usually crust and heal in 1 week. Immunosuppressed patients may have unusual variants, including verrucous or nodular herpes lesions at typical sites of involvement. Lesions of herpes simplex must be distinguished from chancroid, syphilis, lymphogranuloma venereum, pyoderma gangrenosum, or trauma.

B. Laboratory Findings

Direct fluorescent antibody slide tests offer rapid, sensitive diagnosis. Viral culture or PCR may also be helpful. Herpes serology is not used in the diagnosis of an acute genital ulcer. Specific HSV-2 serology by Western blot assay or ELISA can determine who is HSV-infected and potentially infectious, but routine HSV-2 screening is not recommended by the USPSTF.



▲ **Figure 6–12. Orolabial herpes simplex showing deroofed blisters (ulcer).** (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Complications

Complications include pyoderma, eczema herpeticum, herpetic whitlow, herpes gladiatorum (epidemic herpes transmitted by contact), proctitis, esophagitis, neonatal infection, keratitis, and encephalitis.

Treatment

A. Systemic Therapy

Three systemic agents are available for the treatment of acute herpes infections: acyclovir, valacyclovir, and famciclovir. All three agents are very effective, and when used properly, virtually nontoxic. Only acyclovir is available for intravenous administration. In the immunocompetent, with the exception of severe orolabial herpes, only genital disease is treated.

1. For first clinical episode—Recommended treatment for the first clinical episodes of herpes simplex includes acyclovir, 400 mg orally five times daily (or 800 mg three times daily); valacyclovir, 1000 mg orally twice daily; or famciclovir, 250 mg orally three times daily; treatment is for 7–10 days, depending on the severity of the outbreak.

2. For mild recurrences—Most cases do not require therapy. Pharmacotherapy of recurrent HSV is of limited benefit, reducing the average outbreak by only 12–24 hours. **To be effective, the treatment must be initiated by the patient at the first sign of recurrence**. If treatment is desired, recurrent genital herpes outbreaks may be treated with 3 days of valacyclovir, 500 mg orally twice daily, 5 days of acyclovir, 200 mg orally five times a day, or 5 days of famciclovir, 125 mg orally twice daily. Valacyclovir, 2 g

twice daily for 1 day, and famciclovir, 1 g once or twice in 1 day, are equally effective short-course alternatives and can abort impending recurrences of both orolabial and genital herpes. The addition of a potent topical corticosteroid three times daily reduces the duration, size, and pain of orolabial herpes treated with an oral antiviral agent.

3. For frequent or severe recurrences—Suppressive treatment reduces recurrences by 85%, viral shedding by more than 90%, and the risk of transmission by 50%. The recommended suppressive doses, taken continuously, are acyclovir, 400 mg orally twice daily; valacyclovir, 500 mg orally once daily; or famciclovir, 125–250 mg orally twice daily. Pritelivir, 100 mg orally once daily, may have superior reduction of viral shedding in HSV-2 compared to valacyclovir, 500 mg orally once daily. Long-term suppression appears safe, and after 5–7 years a substantial proportion of patients can discontinue treatment.

Sunscreens are useful adjuncts in preventing sun-induced orolabial recurrences. A preventive antiviral medication should be started beginning 24 hours prior to UV light exposure, dental surgery, or orolabial cosmetic surgery. The use of latex condoms and patient education have proved effective in reducing genital herpes transmission in some but not all studies. No single or combination intervention absolutely prevents transmission.

B. Local Measures

Topical therapy has limited efficacy and is generally not recommended because evidence shows that it minimally reduces skin healing time.

Prognosis

Aside from the complications described above, recurrent attacks last several days, and patients recover without sequelae.

Damour A et al. Eczema herpeticum: clinical and pathophysiological aspects. Clin Rev Allergy Immunol. 2020;59:1. [PMID: 31836943]

HERPES ZOSTER (Shingles)

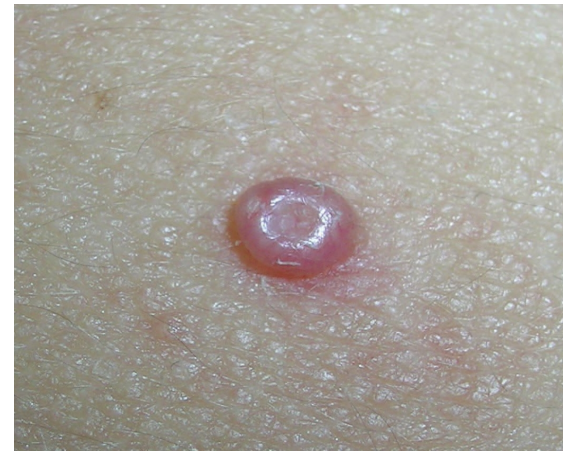
See Chapter 32.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum, caused by a poxvirus, presents as single or multiple dome-shaped, waxy papules 2–5 mm in diameter that are umbilicated (Figure 6–13). Lesions at first are firm, solid, and flesh-colored but upon reaching maturity become soft, whitish, or pearly gray and may suppurate. The principal sites of involvement are the face, lower abdomen, and genitals.

The lesions are autoinoculable and spread by wet skin-to-skin contact. In sexually active individuals, they may be confined to the penis, pubis, and inner thighs and are considered a sexually transmitted infection.

Molluscum contagiosum is common in patients with AIDS, usually with a helper T-cell count less than 100/mcL (0.1×10^9/L). Extensive lesions tend to develop over the face and neck as well as in the genital area.



▲ **Figure 6–13. Umbilicated—molluscum.** (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 3nd ed. McGraw-Hill, 2019.)

The diagnosis is easily established in most instances because of the distinctive central umbilication of the dome-shaped lesion. Estimated time to remission is 13 months. The best treatment is by curettage or applications of liquid nitrogen as for warts—but more briefly. When lesions are frozen, the central umbilication often becomes more apparent. Light electrosurgery with a fine needle is also effective. Cantharadin (applied in the office and then washed off by the patient 4 hours later) is a safe and effective option. Another treatment option is 10% or 15% potassium hydroxide solution applied twice daily until lesions clear. Salicylic acid, podophyllotoxin, tretinoin, imiquimod, and intralesional immunotherapy are additional treatment options. Physical destruction with pulsed dye laser or via extraction of molluscum bodies with a comedone extractor or currette is also effective. Lesions are difficult to eradicate in patients with AIDS unless immunity improves; however, with highly effective antiretroviral treatment, molluscum usually spontaneously clears.

Wells A et al. Intralesional immunotherapy for molluscum contagiosum: a review. Dermatol Ther. 2020;33:e14386. [PMID: 33044025]

WARTS

ESSENTIALS OF DIAGNOSIS

- Verrucous papules anywhere on the skin or mucous membranes, usually not > 1 cm in diameter.
- Prolonged incubation period (average 2–18 months).
- Spontaneous "cures" of common warts in 50% at 2 years.
- "Recurrences" (new lesions) are frequent.

General Considerations

Warts (common, plantar, and genital [condylomata acuminata]) are caused by HPVs. Typing of HPV lesions is not a part of standard medical evaluation except in the case of anogenital dysplasia.

Clinical Findings

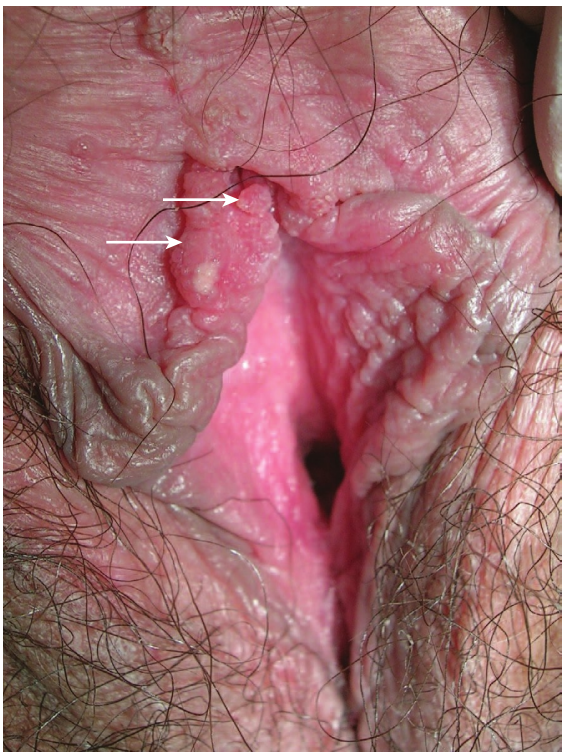
There are usually no symptoms. Tenderness on pressure occurs with plantar warts; itching occurs with anogenital warts (Figure 6–14). Flat warts are most evident under oblique illumination. Periungual warts may be dry, fissured, and hyperkeratotic and may resemble hangnails. Plantar warts resemble plantar corns or calluses.

Differential Diagnosis

Some warty-looking lesions are actually seborrheic keratosis, hypertrophic actinic keratoses or squamous cell carcinomas. Some genital warty lesions are condylomata lata of secondary syphilis. Molluscum contagiosum lesions are pearly with a central dell. In AIDS, wart-like lesions may be caused by varicella zoster virus.

Prevention

Administration of a vaccine against certain anogenital HPV types (including 6, 11, 16, 18, 31, 33, 45, 52, and 58) can prevent infection with these wart types and reduce anogenital, oropharyngeal, and cervical cancer. It is recommended for teenagers and young adults, men who have sex with men, and immunocompromised patients (see Chapters 1 and 18). There may be a role for adjuvant vaccination in HPV-infected patients.



▲ **Figure 6–14. Condylomata acuminata around the clitoris, labia minor, and opening of the vagina.** (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Treatment

Treatment is aimed at inducing "wart-free" intervals for as long as possible without scarring, since no treatment can guarantee a remission or prevent recurrences. In immunocompromised patients, the goal is to control the size and number of lesions present. Certain types (HPV 1) are more responsive to treatment than others (eg, HPV 2, HPV 27).

A. Treatment of Nongenital Warts

For common warts of the hands, patients are usually offered liquid nitrogen or keratolytic agents. The former may work in fewer treatments but requires office visits and is painful.

1. Liquid nitrogen—Liquid nitrogen cryotherapy is applied to achieve a thaw time of 30–45 seconds. Two freeze-thaw cycles are given every 2–4 weeks for several visits. Scarring will occur if it is used incorrectly. Liquid nitrogen may cause permanent depigmentation in darkly pigmented individuals.

2. Keratolytic agents and occlusion—Salicylic acid products may be used against common warts or plantar warts. They are applied, then occluded. Plantar warts may be treated by applying a 40% salicylic acid plaster after paring. The plaster may be left on for 5–6 days, then removed, the lesion pared down, and another plaster applied. Although it may take weeks or months to eradicate the wart, the method is safe and effective with almost no side effects. Chronic occlusion alone with water-impermeable tape (duct tape, adhesive tape) is less effective than cryotherapy.

3. Operative removal—Plantar warts may be removed by blunt dissection.

4. Laser therapy—The CO_2 laser can be effective for treating recurrent warts, periungual warts, plantar warts, and genital warts. It leaves open wounds that must fill in with granulation tissue over 4–6 weeks and is best reserved for warts resistant to all other modalities. Lasers with emissions of 585, 595, or 532 nm may also be used every 3–4 weeks to ablate common, plantar, facial, and anogenital warts but are not more effective than cryotherapy in controlled trials. Photodynamic therapy can be considered in refractory widespread flat warts.

5. Immunotherapy—Squaric acid dibutylester may be applied 1–5 times weekly in a concentration of 0.2–2% directly to the warts to induce a mild contact dermatitis. Between 60% and 80% of warts clear over 10–20 weeks. Injection of *Candida* antigen starting at 1:50 dilution and repeated every 3–4 weeks may be similarly effective in stimulating immunologic regression of common and plantar warts.

6. Other agents—Bleomycin (1 unit/mL), injected into common and plantar warts has been shown to have a high cure rate. It should be used with caution on digital warts because of the potential complications of Raynaud phenomenon, nail loss, and terminal digital necrosis. 5-Fluorouracil 5% cream applied once or twice daily, usually with occlusion, has similar efficacy to other treatment methods. Topical or intralesional cidofovir may be effective in treating recalcitrant lesions, especially in immunocompromised patients.

7. Physical modalities—Soaking warts in hot (42.2°C) water for 10–30 minutes daily for 6 weeks has resulted in involution in some cases.

B. Treatment of Genital Warts

1. Liquid nitrogen—Cryotherapy is first-line clinician-applied surgical treatment for genital warts. Liquid nitrogen cryotherapy is applied to achieve a thaw time of 30–45 seconds. Two freeze-thaw cycles are given every 2–4 weeks for several visits. Scarring will occur if it is used incorrectly. Liquid nitrogen may cause permanent depigmentation in pigmented individuals.

2. Podophyllum resin—For genital warts, the purified active component of the podophyllum resin, podofilox, is applied by the patient twice daily 3 consecutive days a week for cycles of 4–6 weeks. It is less irritating and more effective than "clinician-applied" podophyllum resin. After a single 4-week cycle, 45% of patients were wart-free but 60% relapsed at 6 weeks. Thus, multiple cycles of treatment are often necessary. Patients unable to obtain the take-home podofilox may be treated in the clinician's office by painting each wart carefully (protecting normal skin) every 2–3 weeks with 25% podophyllum resin (podophyllin) in compound tincture of benzoin.

3. Imiquimod—A 5% cream of this local interferon inducer has moderate activity in clearing external genital warts. Treatment is once daily on 3 alternate days per week. Response may be slow. Complete clearing of lesions occurs in 77% of women and 40% of men with 13% recurrences in the short term.

Although imiquimod is considerably more expensive than podophyllotoxin, it is the "patient-administered" treatment of choice for external genital warts in women due to its high response rate and safety. In men, podophyllin resin remains the preferred initial treatment due to its more rapid response, lower cost, and similar efficacy; imiquimod is used for recurrences or refractory cases. Imiquimod has no demonstrated efficacy for—and should not be used to treat—plantar or common warts.

4. Sinecatechins—Derived from green tea extract, sinecatechins (10% or 15%) is FDA approved for the treatment of anogenital warts. Application three times daily for 16 weeks achieves clearance rates from 40% to 81%, with the 15% formulation resulting in higher efficacy.

5. Operative removal—For pedunculated or large genital warts, snip biopsy (scissors) removal followed by light electrocautery is more effective than cryotherapy.

6. Laser therapy—See Treatment of Nongenital Warts, above. For genital warts, it has not been shown that laser therapy is more effective than electrosurgical removal. Photodynamic therapy can be considered in refractory genital warts.

Prognosis

There is a striking tendency to develop new lesions. Warts may disappear spontaneously or may be unresponsive to treatment. Combining therapies (eg, liquid nitrogen plus immunotherapy) may improve therapeutic response.

Anshelevich EE et al. Intralesional cidofovir for treatment of recalcitrant warts in both immunocompetent and immunocompromised patients: a retrospective analysis of 58 patients. J Am Acad Dermatol. 2021;84:206. [PMID: 32348821]

García-Oreja S et al. Topical treatment for plantar warts: a systematic review. Dermatol Ther. 2021;34:e14621. [PMID: 33263934]

Jung JM et al. Topically applied treatments for external genital warts in nonimmunocompromised patients: a systematic review and network meta-analysis. Br J Dermatol. 2020;183:24. [PMID: 31675442]

O'Mahony C et al. Position statement for the diagnosis and management of anogenital warts. J Eur Acad Dermatol Venereol. 2019;33:1006. [PMID: 30968980]

BACTERIAL INFECTIONS

IMPETIGO

ESSENTIALS OF DIAGNOSIS

- Superficial blisters filled with purulent material that rupture easily.
- Crusted superficial erosions.
- Positive Gram stain and bacterial culture.

General Considerations

Impetigo is a contagious and autoinoculable infection of the skin (epidermis) caused by staphylococci or streptococci.

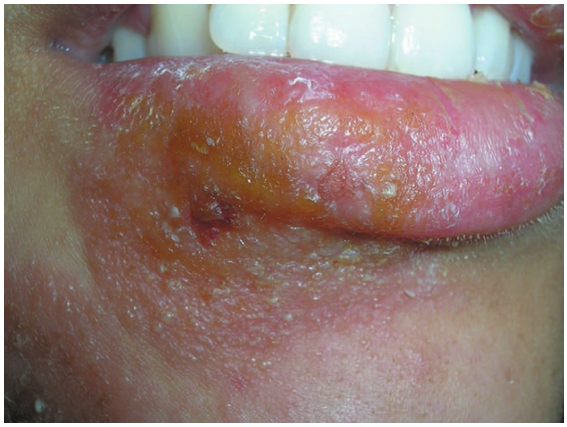
Clinical Findings

A. Symptoms and Signs

The lesions consist of macules, vesicles, bullae, pustules, and honey-colored crusts that when removed leave denuded red areas (Figure 6–15). The face and other exposed parts are most often involved. Ecthyma is a deeper form of impetigo caused by staphylococci or streptococci, with ulceration and scarring that occurs frequently on the extremities.

B. Laboratory Findings

Gram stain and culture confirm the diagnosis. In temperate climates, most cases are associated with *S aureus* infection. *Streptococcus* species are more common in tropical infections.



▲ **Figure 6–15. Typical honey-crusted plaque on the lip of an adult with impetigo.** (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

Differential Diagnosis

The main differential diagnoses of honey-colored crusting are acute allergic contact dermatitis and herpes simplex. Contact dermatitis may be suggested by the history or by linear distribution of the lesions, and culture should be negative for staphylococci and streptococci. Herpes simplex infection usually presents with grouped vesicles or discrete erosions and may be associated with a history of recurrences. Viral cultures are positive.

Treatment

Soaks and scrubbing can be beneficial, especially in unroofing lakes of pus under thick crusts. Topical agents, such as mupirocin, ozenoxacin, and retapamulin, are first-line treatment options for infections limited to small areas. In widespread cases, or in immunosuppressed individuals, systemic antibiotics are indicated. Cephalexin, 250 mg orally four times daily, is usually effective. Community-associated methicillin-resistant *S aureus* (CA-MRSA) may cause impetigo, for which initial treatment may include doxycycline (100 mg orally twice daily) or trimethoprim-sulfamethoxazole (TMP-SMZ, double-strength tablet orally twice daily). Recurrent impetigo is associated with nasal carriage of *S aureus* and is treated with rifampin, 300 mg orally twice daily for 5 days. Intranasal mupirocin ointment twice daily for 14 days eliminates most MRSA strains. Bleach baths (¼ to ½ cup per 20 liters of bathwater for 15 minutes three to five times weekly) for all family members and the use of dilute household bleach to clean showers and other bath surfaces may help reduce the spread. Infected individuals should not share towels with household members. Among hospitalized patients colonized with MRSA, decolonization with chlorhexidine washes combined with nasal mupirocin for 5 days twice per month for 6 months resulted in 30% lower risk of MRSA infection than education alone.

Schachner LA et al. Treatment of impetigo and antimicrobial resistance. J Drugs Dermatol. 2021;20:366. [PMID:33852242]

FOLLICULITIS (Including Sycosis)

ESSENTIALS OF DIAGNOSIS

- Itching and burning in hairy areas.
- Pustule surrounding and including the hair follicle.

General Considerations

Folliculitis has multiple causes. It is frequently caused by staphylococcal infection and may be more common in the diabetic patient. When the lesion is deep-seated, chronic, and recalcitrant on the head and neck, it is called **sycosis.**

Gram-negative folliculitis, which may develop during antibiotic treatment of acne, may present as a flare of acne pustules or nodules. *Klebsiella, Enterobacter, Escherichia coli*, and *Proteus* have been isolated from these lesions.

Hot tub folliculitis (*Pseudomonas* folliculitis), caused by *Pseudomonas aeruginosa*, is characterized by pruritic or tender follicular, pustular lesions occurring within 1–4 days after bathing in a contaminated hot tub, whirlpool, or swimming pool. Flu-like symptoms may be present. Rarely, systemic infections may result. Neutropenic patients should avoid these exposures.

Nonbacterial folliculitis may also be caused by friction and oils. Occlusion, perspiration, and chronic rubbing (eg, from tight-fitting clothing or heavy fabrics on the buttocks and thighs) can worsen this type of folliculitis.

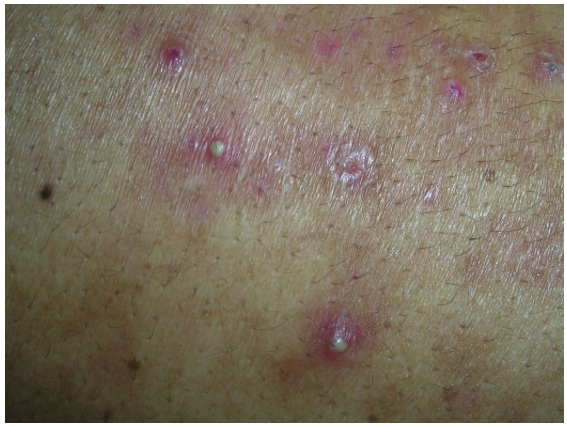
Steroid acne may be seen during topical or systemic corticosteroid therapy and presents as eruptive monomorphous papules and papulopustules on the face and trunk. It responds to topical benzoyl peroxide.

Eosinophilic folliculitis is a sterile folliculitis that presents with urticarial papules with prominent eosinophilic infiltration. It is most common in immunosuppressed patients, especially those with AIDS. It may appear first with institution of highly active antiretroviral therapy (ART) and be mistaken for a drug eruption.

Pseudofolliculitis is caused by ingrowing of tightly curled hairs in the beard area. In this entity, the papules and pustules are located at the side of and not in follicles. It may be treated by growing a beard, by using chemical depilatories, or by shaving with a foil-guard razor. Medically indicated laser hair removal is dramatically beneficial in patients with pseudofolliculitis and can be done on patients of any skin color.

Pityrosporum folliculitis presents as 1- to 2-mm pruritic pink papulopustules on the upper trunk, hairline, and arms. It is often pruritic and tends to develop during periods of excessive sweating. It can also occur in immunosuppressed patients.

Demodex folliculitis is caused by the mite *Demodex folliculorum*. It presents as 1–2 mm papules and pustules on an erythematous base, often on the background of



▲ **Figure 6–16.** Bacterial folliculitis. Hair emanating from the center of the pustule is the clinical hallmark of folliculitis. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

rosacea-like changes, in patients who have not responded to conventional treatment for rosacea. It is more common in immunosuppressed patients. KOH from the pustules will demonstrate *Demodex folliculorum* mites.

Clinical Findings

The symptoms range from slight burning and tenderness to intense itching. The lesions consist of pustules of hair follicles (Figure 6–16).

Differential Diagnosis

It is important to differentiate bacterial from nonbacterial folliculitis. The history is important for pinpointing the causes of nonbacterial folliculitis, and a Gram stain and culture are indispensable. One must differentiate bacterial folliculitis from acne vulgaris or pustular miliaria (heat rash) and from other infections of the skin, such as impetigo or *Pityrosporum* folliculitis. Eosinophilic folliculitis in AIDS often requires biopsy for diagnosis.

Complications

Abscess formation is the major complication of bacterial folliculitis.

Prevention

Correct any predisposing local causes, such as oils or friction. Be sure that the water in hot tubs and spas is treated properly. If staphylococcal folliculitis is persistent, treatment of nasal or perineal carriage with rifampin, 600 mg daily for 5 days, or with topical mupirocin ointment 2% twice daily for 5 days, may help. Prolonged oral clindamycin, 150–300 mg/day for 4–6 weeks, or oral TMP-SMZ given 1 week per month for 6 months can be effective in preventing recurrent staphylococcal folliculitis and furunculosis. Bleach baths (¼ to ½ cup per 20 liters of bathwater for 15 minutes three to five times weekly) may reduce cutaneous staphylococcal carriage and not contribute to antibiotic resistance. Control of blood glucose in diabetes may reduce infections.

Treatment

A. Local Measures

Anhydrous ethyl alcohol containing 6.25% aluminum chloride, applied three to seven times weekly to lesions, may be helpful, especially for chronic frictional folliculitis of the buttocks. Topical antibiotics are generally ineffective if bacteria have invaded the hair follicle but may be prophylactic if used as an aftershave in patients with recurrent folliculitis after shaving.

B. Specific Measures

Pseudomonas folliculitis clears spontaneously in nonneutropenic patients if the lesions are superficial. It may be treated with ciprofloxacin, 500 mg orally twice daily for 5 days.

Systemic antibiotics are recommended for bacterial folliculitis due to other organisms. Extended periods of treatment (4–8 weeks or more) with antistaphylococcal antibiotics are required if infection involves the scalp or densely hairy areas, such as the axilla, beard, or groin (see Table 30–4).

Gram-negative folliculitis in acne patients may be treated with isotretinoin in compliance with all precautions discussed above (see Acne Vulgaris).

Eosinophilic folliculitis may be treated initially by the combination of potent topical corticosteroids and oral antihistamines. In more severe cases, treatment is with one of the following: topical permethrin (application for 12 hours every other night for 6 weeks); itraconazole, 200–400 mg orally daily; UVB or PUVA phototherapy; or isotretinoin, 0.5 mg/kg/day orally for up to 5 months. A remission may be induced by some of these therapies, but long-term treatment may be required.

Pityrosporum folliculitis is treated with topical sulfacetamide lotion twice a day, alone or in combination with oral itraconazole or fluconazole.

Demodex folliculitis can be treated until cleared with topical 5% permethrin applied every other night; oral ivermectin, 200 mcg/kg once weekly; oral metronidazole, 500 mg once daily or 250 mg three times daily; or topical ivermectin or metronidazole.

Prognosis

Bacterial folliculitis is occasionally stubborn and persistent, requiring prolonged or intermittent courses of antibiotics.

Chaitidis N et al. Oral treatment with/without topical treatment vs topical treatment alone in *Malassezia* folliculitis patients: a systematic review and meta-analysis. Dermatol Ther. 2020;33:e13460. [PMID: 32319163]

Lin HS et al. Interventions for bacterial folliculitis and boils (furuncles and carbuncles). Cochrane Database Syst Rev. 2021;2:CD013099. [PMID: 33634465]

FURUNCULOSIS (Boils) & CARBUNCLES

ESSENTIALS OF DIAGNOSIS

- Extremely painful inflammatory abscess based on a hair follicle.
- Coagulase-positive *S aureus* is the causative organism.
- Predisposing condition (diabetes mellitus, HIV disease, injection drug use) sometimes present.

General Considerations

A **furuncle (boil)** is a deep-seated infection (abscess) caused by *S aureus* that involves the hair follicle and adjacent subcutaneous tissue. The most common sites of occurrence are the hairy parts exposed to irritation and friction, pressure, or moisture. Because the lesions are autoinoculable, they are often multiple. Diabetes mellitus (especially if using insulin injections), injection drug use, allergy injections, and HIV disease all increase the risk of staphylococcal infections by increasing the rate of carriage. Certain other exposures including hospitalization, athletic teams, prisons, military service, and homelessness may also increase the risk of infection.

A **carbuncle** consists of several furuncles developing in adjoining hair follicles and coalescing to form a conglomerate, deeply situated mass with multiple drainage points.

Recurrent furunculosis (three or more episodes in 12 months) tends to occur in those with direct contact with other infected individuals, especially family members.

Clinical Findings

A. Symptoms and Signs

Pain and tenderness may be prominent. The abscess is either rounded or conical. It gradually enlarges, becomes fluctuant, and then softens and opens spontaneously after a few days to 1–2 weeks to discharge a core of necrotic tissue and pus. The inflammation occasionally subsides before necrosis occurs.

B. Laboratory Findings

There may be slight leukocytosis. Pus can be cultured to rule out MRSA or other bacteria. Culture of the anterior nares and anogenital area (including the rectum to test for GI carriage) may identify chronic staphylococcal carriage in cases of recurrent cutaneous infection.

Differential Diagnosis

The most common entity in the differential is an inflamed **epidermal inclusion cyst** that suddenly becomes red, tender, and expands greatly in size over one to a few days. The history of a prior cyst in the same location, the presence of a clearly visible cyst orifice, and the extrusion of malodorous cheesy material (rather than purulent material) helps in the diagnosis. Tinea profunda (deep dermatophyte infection of the hair follicle) may simulate recurrent furunculosis. Furunculosis is also to be distinguished from deep mycotic infections, such as sporotrichosis; from other bacterial infections, such as anthrax and tularemia (rare); from atypical mycobacterial infections; and from acne cysts. Hidradenitis suppurativa (acne inversa) presents with recurrent tender, sterile abscesses in the axillae and groin, on the buttocks, or below the breasts. The presence of old scars or sinus tracts plus negative cultures suggests this diagnosis.

Complications

Serious and sometimes fatal complications of staphylococcal infection such as septicemia can occur.

Prevention

Identifying and eliminating the source of infection is critical to prevent recurrences after treatment. The source individual may have chronic dermatitis or be an asymptomatic carrier of MRSA. Nasal carriage of MRSA and the number of children in a household are risk factors for transmission between household members. Local measures, such as meticulous handwashing; no sharing of towels, clothing, and personal hygiene products; avoiding loofas or sponges in the bath or shower; changing underwear, sleepwear, towels, and washcloths daily; aggressive scrubbing of showers, bathrooms, and surfaces with bleach; bleach baths (¼–½ cup per 20 liters of bathwater for 15 minutes three to five times weekly), 4% chlorhexidine washes, and isolation of infected patients who reside in institutions to prevent spread are all effective measures.

Treatment

A. Specific Measures

Incision and drainage are recommended for all loculated suppurations and are the mainstay of therapy. Systemic antibiotics are usually given. Patients who receive antibiotics (specifically, TMP-SMZ [160/800 or 320/1600 mg orally twice a day for 10 days or 7 days, respectively] or clindamycin [300 mg orally three times daily for 10 days]) at the time of drainage have higher cure and lower reinfection rates. Other oral antibiotic options include dicloxacillin or cephalexin, 1 g daily in divided doses for 10 days. For suspected MRSA, doxycycline 100 mg twice daily, TMP-SMZ double-strength one tablet twice daily, clindamycin 150–300 mg twice daily, and linezolid 400 mg twice daily for 7–10 days are effective. Recurrent furunculosis may be effectively treated with a combination of cephalexin (250–500 mg orally four times daily) or doxycycline (100 mg orally twice daily) for 2–4 weeks plus either rifampin (300 mg orally twice daily for 5 days) or long-term clindamycin (150–300 mg orally daily for 1–2 months). Shorter courses of antibiotics (7–14 days) plus longer-term daily 4% chlorhexidine whole body washing and intranasal, axilla, and anogenital mupirocin or retapamulin may also cure recurrent furunculosis. Oral vancomycin (1 g twice daily for 5 days) can treat GI carriage of *S aureus*. Family members, pets, and intimate contacts may need evaluation for

staphylococcal carrier state and perhaps concomitant treatment. Stopping high-risk behavior, such as injection drug use, can also prevent recurrence.

B. Local Measures

Immobilize the part and avoid over-manipulation of inflamed areas. Use moist heat to help larger lesions "localize." Use surgical incision and drainage after the lesions are "mature."

Prognosis

Recurrent crops may occur for months or years.

Lin HS et al. Interventions for bacterial folliculitis and boils (furuncles and carbuncles). Cochrane Database Syst Rev. 2021;2:CD013099. [PMID: 33634465]

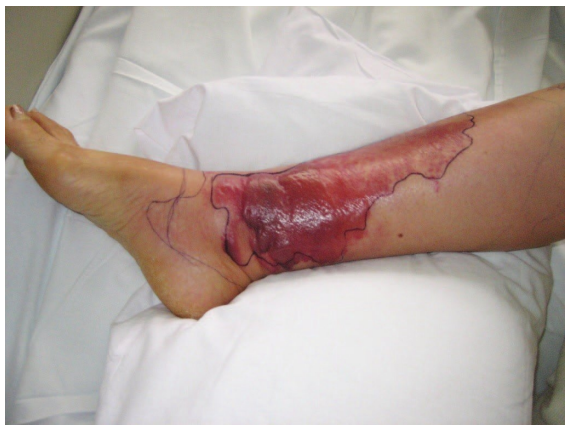
CELLULITIS

ESSENTIALS OF DIAGNOSIS

- Edematous, expanding, erythematous, warm plaque with or without vesicles or bullae.
- Lower leg is frequently involved.
- Pain, chills, and fever are commonly present.
- Septicemia may develop.

General Considerations

Cellulitis, a diffuse spreading infection of the dermis and subcutaneous tissue, is usually on the lower leg (Figure 6–17) and most commonly due to gram-positive cocci, especially group A beta-hemolytic streptococci and *S aureus*. Rarely, gram-negative rods or even fungi can produce a similar picture. In otherwise healthy persons, the most common portal of entry for lower leg cellulitis is interdigital tinea pedis with fissuring. Other diseases that predispose to cellulitis are prior episodes of cellulitis, chronic edema, venous insufficiency with secondary edema, lymphatic obstruction, saphenectomy, and other perturbations of the skin barrier. Bacterial cellulitis is almost never bilateral.



▲ **Figure 6–17. Cellulitis.** (Used, with permission, from Lindy Fox, MD.)

Clinical Findings

A. Symptoms and Signs

Cellulitis begins as a tender small patch. Swelling, erythema, and pain are often present. The lesion expands over hours, so that from onset to presentation is usually 6 to 36 hours. As the lesion grows, the patient becomes more ill with progressive chills, fever, and malaise. Lymphangitis and lymphadenopathy are often present. If septicemia develops, hypotension may develop, followed by shock.

B. Laboratory Findings

Leukocytosis or neutrophilia (left shift) may be present early in the course. Blood cultures are positive in only 4% of patients. If a central ulceration, pustule, or abscess is present, culture may be of value. Aspiration of the advancing edge has a low yield (less than 20%) and is usually not performed. In immunosuppressed patients, or if an unusual organism is suspected and there is no loculated site to culture, a full-thickness skin biopsy should be sent for routine histologic evaluation and for culture (bacterial, fungal, and mycobacterial). If a primary source for the infection is identified (wound, leg ulcer, toe web intertrigo), cultures from these sites isolate the causative pathogen in half of cases and can be used to guide antibiotic therapy.

Differential Diagnosis

Two potentially life-threatening entities that can mimic cellulitis (ie, present with a painful, red, swollen lower extremity) include DVT and necrotizing fasciitis. The diagnosis of necrotizing fasciitis should be suspected in a patient who has a toxic appearance, bullae, crepitus or anesthesia of the involved skin, overlying skin necrosis, and laboratory evidence of rhabdomyolysis (elevated creatine kinase) or disseminated intravascular coagulation. While these findings may be present with severe cellulitis and bacteremia, it is essential to rule out necrotizing fasciitis because rapid surgical debridement is essential. Other noninfectious skin lesions that may resemble cellulitis are termed "pseudocellulitis." Diseases in this differential include sclerosing panniculitis, an acute, exquisitely tender red plaque on the medial lower legs above the malleolus in patients with venous stasis or varicosities, and acute severe contact dermatitis on a limb, which produces erythema, vesiculation, and edema, as seen in cellulitis, but with itching instead of pain. Bilateral lower leg bacterial cellulitis is exceedingly rare, and other diagnoses, especially severe stasis dermatitis (see Figure 12–2), should be considered in this setting. Severe lower extremity stasis dermatitis usually develops over days to weeks rather than hours as with cellulitis. It is also not as tender to palpation as cellulitis. Cryptococcal cellulitis in the organ transplant recipient is often bilateral. The ALT-70 is a predictive model to diagnose cellulitis or a cellulitis mimic and to provide guidance about when a dermatology consultation is needed.

The ALT-70 variables are asymmetry (3 points), leukocytosis of 10,000/mcL (10×10^9/L) or more at presentation (2 points), tachycardia above 90 beats per minute (1 point), and age 70 years or older (1 point). An ALT-70 score above 5 points carries more than an 82% chance of a true cellulitis while a score below 2 points suggests a greater than 83% chance of a cellulitis mimicker.

Treatment

Intravenous or parenteral antibiotics may be required for the first 2–5 days, with adequate coverage for *Streptococcus* and *Staphylococcus*. Methicillin-susceptible *S aureus* (MSSA) can be treated with nafcillin, cefazolin, clindamycin, dicloxacillin, cephalexin, doxycycline, or TMP-SMZ. If MRSA is suspected or proven, treatment options include vancomycin, linezolid, clindamycin, daptomycin, doxycycline, or TMP-SMZ. In mild cases or following the initial parenteral therapy, oral dicloxacillin or cephalexin, 250–500 mg four times daily for 5–10 days, is usually adequate. In patients in whom intravenous treatment is not instituted, the first dose of oral antibiotic can be doubled to achieve high blood levels rapidly. In patients with recurrent lower leg cellulitis (three to four episodes per year), oral penicillin 250 mg twice daily or oral erythromycin 250–500 mg twice daily can decrease the risk of recurrence. Prior episodes of cellulitis, lymphedema, chronic venous insufficiency, peripheral vascular disease, and DVT are associated with an increased risk of recurrent cellulitis. Additional measures to prevent recurrences include compression, treating toe web intertrigo and tinea pedis, and controlling venous insufficiency.

When to Admit

- Severe local symptoms and signs.
- Signs of sepsis.
- Elevated WBC count of 10,000/mcL (10×10^9/L) or more with marked left shift. Failure to respond to oral antibiotics.

Klotz C et al. Adherence to antibiotic guidelines for erysipelas or cellulitis is associated with a favorable outcome. Eur J Clin Microbiol Infect Dis. 2019;38:703. [PMID: 30685804]
Rrapi R et al. Cellulitis: a review of pathogenesis, diagnosis, and management. Med Clin North Am. 2021;105:723. [PMID: 34059247]
Webb E et al. Compression therapy to prevent recurrent cellulitis of the leg. N Engl J Med. 2020;383:630. [PMID: 32786188]

ERYSIPELAS

ESSENTIALS OF DIAGNOSIS

- Edematous, circumscribed, hot, erythematous area, with raised advancing border.
- Central face or lower extremity frequently involved.
- Pain and systemic toxicity may be striking.

General Considerations

Erysipelas is a superficial form of cellulitis that is caused by beta-hemolytic streptococci.

Clinical Findings

A. Symptoms and Signs

The symptoms are pain, malaise, chills, and moderate fever. A bright red spot appears and then spreads to form a tense, sharply demarcated, glistening, smooth, hot plaque. The sharp margin characteristically makes noticeable advances in days or even hours. The lesion is edematous with a raised edge and may pit slightly with the finger. Vesicles or bullae occasionally develop on the surface. The lesion does not usually become pustular or gangrenous and heals without scar formation. Breaks in the skin often provide a portal of entry for the organism. On the face, erysipelas begins near a fissure at the angle of the nose. On the lower extremity, tinea pedis with interdigital fissuring is a common portal of entry.

B. Laboratory Findings

Leukocytosis is almost invariably present; blood cultures may be positive.

Differential Diagnosis

Erysipeloid is a benign bacillary infection by *Erysipelothrix rhusiopathiae* that produces cellulitis of the skin of the fingers or the backs of the hands in fishermen and meat handlers.

Complications

Unless erysipelas is promptly treated, death may result from bacterial dissemination, particularly in older adults.

Treatment

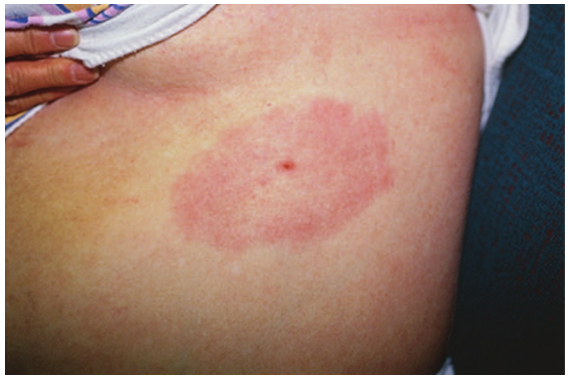
Intravenous antibiotics effective against group A beta-hemolytic streptococci and staphylococci should be considered, but outpatient treatment with oral antibiotics has demonstrated equal efficacy. Oral regimens include a 7-day course with penicillin VK (250 mg), dicloxacillin (250 mg), or a first-generation cephalosporin (250 mg) four times a day. Clindamycin (250 mg twice daily orally for 7–14 days) is an option for penicillin-allergic patients.

Prognosis

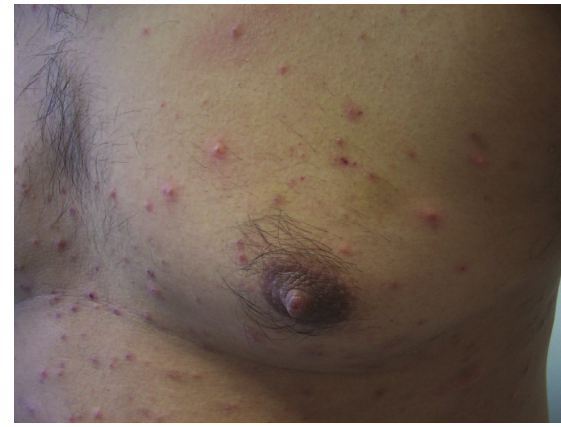
With appropriate treatment, rapid improvement is expected. The presence of lymphedema carries the greatest risk of recurrence.

ERYTHEMA MIGRANS

Erythema migrans is a unique cutaneous eruption that characterizes the localized or generalized early stage of Lyme disease (caused by *Borrelia burgdorferi*) (Figure 6–18) (see also Chapter 34).



▲ **Figure 6–18.** Erythema migrans on trunk. Annular plaque with central clearing and central puncta from the bite. (Reproduced, with permission, from Soutor, Hordinsky MK. *Clinical Dermatology.* The McGraw-Hill Companies; 2013.)



▲ **Figure 6–19.** Scabies. A polymorphic eruption of papulovesicles and excoriated papules scattered on the chest. (Used, with permission, from Kanade Shinkai, MD.)

PARASITIC INFESTATIONS

SCABIES

ESSENTIALS OF DIAGNOSIS

- Generalized very severe itching; infestation usually spares the head and neck.
- Burrows, vesicles, and pustules, especially on finger webs and in wrist creases.
- Mites, ova, and brown dots of feces (scybala) visible microscopically.
- Red papules or nodules on the scrotum and on the penile glans and shaft are pathognomonic.

General Considerations

Scabies is caused by infestation with *Sarcoptes scabiei*, affecting over 200 million people worldwide. Close physical contact for 15–20 minutes with an infected person is the typical mode of transmission. However, scabies may be acquired by contact with the bedding of an infested individual. Facility-associated scabies is common, primarily in long-term care facilities, and misdiagnosis is common. Index patients are usually elderly and immunosuppressed. When these patients are hospitalized, hospital-based epidemics can occur and are difficult to eradicate when health care workers become infected and spread the infestation to other patients.

Clinical Findings

A. Symptoms and Signs

Itching is almost always present and can be severe. The lesions consist of generalized excoriations with small pruritic vesicles, pustules, and "burrows" in the interdigital spaces of the hands and feet, on the heels of the palms, wrists, elbows, umbilicus, around the axillae, on or around the areolae (Figure 6–19), or on the penile shaft and scrotum in men. The burrow appears as a short irregular mark, 2–3 mm long and the width of a hair. Characteristic nodular lesions may occur on the scrotum or penis and along the posterior axillary line. The infestation usually spares the head and neck (though these areas may be involved in infants, older adults, and patients with AIDS).

Hyperkeratotic or crusted scabies presents as thick flaking scale. These areas contain millions of mites, and these patients are highly infectious. Pruritus is often absent. Patients with widespread hyperkeratotic scabies are at risk for superinfection with *S aureus*, which in some cases progresses to sepsis if left untreated. Crusted scabies is the cause of 83% of scabies outbreaks in institutions.

B. Laboratory Findings

The diagnosis should be confirmed by microscopic demonstration of the organism, ova, or feces in a mounted specimen, examined with tap water, mineral oil, or KOH. Best results are obtained when multiple lesions are scraped, choosing the best unexcoriated lesions from interdigital webs, wrists, elbows, or feet. A No. 15 blade is used to scrape each lesion until it is flat. Patients with crusted/hyperkeratotic scabies must be evaluated for immunosuppression (especially HIV and HTLV-1 infections) if no iatrogenic cause of immunosuppression is present. Patients with hyperkeratotic scabies and associated bacterial superinfection may have laboratory findings consistent with infection and, if severe, sepsis.

Differential Diagnosis

Scabies must be distinguished from the various forms of pediculosis, from bedbug and flea bites, and from other causes of pruritus.

Treatment & Prognosis

Treatment is aimed at killing scabies mites and controlling the dermatitis, which can persist for months after effective

eradication of the mites. Bedding and clothing should be laundered or set aside for 14 days in plastic bags. High heat (60°C) is required to kill the mites and ova. Treatment is aimed at all infected persons in a family or institutionalized group. Otherwise, reinfestations will likely occur, which is why scabies in nursing home patients, institutionalized or mentally impaired patients, and AIDS patients may be much more difficult to treat.

1. Permethrin 5% cream—Treatment with permethrin, a highly effective and safe agent, consists of a single application from the neck down for 8–12 hours then washed off, repeated in 1 week. Patients often continue to itch for several weeks after treatment. Use of triamcinolone 0.1% cream helps resolve the dermatitis.

Pregnant patients should be treated only if they have documented scabies. Permethrin 5% cream once for 12 hours—or 5% or 6% sulfur in petrolatum applied nightly for 3 nights from the collarbones down—may be used.

Most failures in normal persons are related to incorrect use or incomplete treatment of the housing unit. In these cases, repeat treatment with permethrin once weekly for 2 weeks, with re-education regarding the method and extent of application, is suggested.

2. Ivermectin—In immunocompetent individuals, 200 mcg/kg orally is effective in about 75% of cases with a single dose and 95% of cases with two doses 2 weeks apart. Since the drug is not ovicidal, the second dose theoretically kills eggs that might have hatched after the first dose was given.

Ivermectin is often used in combination with permethrin. In immunosuppressed persons and those with crusted (hyperkeratotic) scabies, multiple doses of ivermectin (every 2 weeks for 2 or 3 doses) plus topical therapy with permethrin every 3 days to once weekly, depending on degree of involvement, may be effective when topical treatment and oral therapy alone fail. A topical keratolytic (urea) should be used to help remove the scale of hyperkeratotic scabies, thereby decreasing the mite load.

Ivermectin can be beneficial in mass treatment to eradicate widespread infection. In endemic areas, mass intervention with ivermectin is effective in controlling both scabies and associated bacterial infections.

If secondary pyoderma is present, it is treated with systemic antibiotics. Staphylococcal superinfection may lead to sepsis. In areas where nephritogenic streptococcal strains are prevalent, infestation with scabies or exposure to scabies-infested dogs may be followed by acute poststreptococcal glomerulonephritis.

Persistent pruritic post-scabietic papules may be treated with mid- to high-potency corticosteroids or with intralesional triamcinolone acetonide (2.5–5 mg/mL).

Engelman D et al. The public health control of scabies: priorities for research and action. Lancet. 2019;394(10192):81. [PMID: 31178154]

Engelman D et al. The 2020 International Alliance for the Control of Scabies consensus criteria for the diagnosis of scabies. Br J Dermatol. 2020;183:808. [PMID: 32034956]

Thomas C et al. Ectoparasites: scabies. J Am Acad Dermatol. 2020;82:533. [PMID: 31310840]

PEDICULOSIS

ESSENTIALS OF DIAGNOSIS

- Pruritus with excoriation.
- Nits on hair shafts; lice on skin or clothes.
- Occasionally, sky-blue macules (maculae ceruleae) on the inner thighs or lower abdomen in pubic lice infestation.

General Considerations

Pediculosis is a parasitic infestation of the skin of the scalp, trunk, or pubic areas. Body lice usually occur among people who live in overcrowded dwellings with inadequate hygiene facilities. Pubic lice may be sexually transmitted. Head lice may be transmitted by shared use of hats or combs. Adults in contact with children with head lice frequently acquire the infestation.

There are three different varieties (1) **pediculosis capitis,** caused by *Pediculus humanus* var *capitis* (head louse); (2) **pediculosis corporis,** caused by *Pediculus humanus* var *corporis* (body louse); and (3) **pediculosis pubis,** caused by *Phthirus pubis* (pubic louse, "crabs").

Head and body lice are 3–4 mm long and similar in appearance. The "body louse" can seldom be found on the body because it comes onto the skin only to feed; it must be looked for in the seams of the clothing. Trench fever, relapsing fever, and typhus are transmitted by the body louse in countries where those diseases are endemic. In the United States, *Bartonella quintana*, the organism that causes trench fever, has been found in lice infesting the homeless population.

Clinical Findings

In body lice infestations, itching may be very intense, and scratching may result in deep excoriations, especially over the upper shoulders, axillae, posterior flanks, and neck. In some cases, only itching is present, with few excoriations seen. Pyoderma (bacterial infection of the skin) may be the presenting sign. Diagnosis is made by examining the seams of clothing for nits and lice. Head lice presents as scalp pruritus often accompanied by erosions on the occipital scalp, posterior neck, and upper back. Diagnosis is made by finding lice on the scalp or small nits resembling pussy willow buds on the scalp hairs close to the skin. Nits are easiest to see above the ears and at the nape of the neck. Pubic lice infestations are occasionally generalized, particularly in hairy individuals; the lice may even be found on the eyelashes and in the scalp. Diagnosis is made by finding lice or nits on pubic hair, body hair, or eyelashes.

Differential Diagnosis

Head lice infestation must be distinguished from seborrheic dermatitis, body lice infestation from scabies and bedbug bites, and pubic lice infestation from anogenital pruritus and eczema.

Treatment

1. Pediculosis capitis—Permethrin 1% cream rinse (Nix) is a topical over-the-counter pediculicide and ovicide. It is applied to the scalp and hair and left on for 8 hours before being rinsed off. Although it is the treatment of choice for head lice, permethrin resistance is common. Malathion lotion 1% (Ovide) is very effective but highly volatile and flammable, so application must be done in a well-ventilated room or out of doors. Topical ivermectin 0.5% lotion, benzyl alcohol 5%, Oxyphthirine® lotion, spinosad 0.9% suspension, dimethicone, and abametapir 0.74% lotion are additional agents that have efficacy against pediculosis capitis; of these, topical ivermectin is the most effective. All infested persons in a household, school, or other facility should ideally be treated at the same time. Other than topical ivermectin, topical therapies should be repeated 7–9 days after the initial treatment. For involvement of eyelashes, petrolatum is applied thickly twice daily for 8 days and the remaining nits plucked off. Systemic treatment options, often used in combination with topical agents, are oral ivermectin (200 mcg/kg orally, repeated in 7 days) (for children older than 5 years and more than 15 kg) and oral TMP-SMZ (10 mg TMP/kg/day and 50 mg SMZ/kg/day divided twice daily for 10 days).

2. Pediculosis corporis—Body lice are treated by disposing of the infested clothing and addressing the patient's social situation.

3. Pediculosis pubis—Application of permethrin rinse 1% for 10 minutes or permethrin cream 5% for 8 hours to the pubis is effective. Sexual contacts should be treated. Clothes and bedclothes should be washed and dried at high temperature.

Coates SJ et al. Ectoparasites: pediculosis and tungiasis. J Am Acad Dermatol. 2020;82:551. [PMID: 31306729]
Gunning K et al. Lice and scabies: treatment update. Am Fam Physician. 2019;99:635. [PMID: 31083883]
Huntington MK et al. Infectious disease: bedbugs, lice, and mites. FP Essent. 2019;476:18. [PMID: 30615406]
Ogbuefi N et al. Common pediatric infestations: update on diagnosis and treatment of scabies, head lice, and bed bugs. Curr Opin Pediatr. 2021;33:410. [PMID: 34074914]

SKIN LESIONS DUE TO OTHER ARTHROPODS

ESSENTIALS OF DIAGNOSIS

- Localized urticarial papules with pruritus.
- Lesions in linear groups of three ("breakfast, lunch, and dinner") are characteristic of bedbugs.
- Furuncle-like lesions containing live arthropods.
- Tender erythematous patches that migrate ("larva migrans").

General Considerations

Some arthropods (eg, mosquitoes and biting flies) are readily detected as they bite. Many others are not because they are too small, because there is no immediate reaction, or because they bite during sleep. Reactions are allergic and may be delayed for hours to days. Patients are most apt to consult a clinician when the lesions are multiple and pruritus is intense.

Many persons react most severely to their earliest contacts with an arthropod, thus presenting with pruritic lesions when traveling, moving into new quarters, etc. Body lice, fleas, bedbugs, and mosquitoes should be considered. Bedbug exposure typically occurs in hotels and in housing with inadequate hygiene but also occurs in stable domiciles. Spiders are often incorrectly believed to be the source of bites, but they rarely attack humans. However, the brown recluse spider (*Loxosceles laeta*, *L reclusa*) may cause severe necrotic reactions and death due to intravascular hemolysis, and the black widow spider (*Latrodectus mactans*) may cause severe systemic symptoms and death. (See also Chapter 38.) The majority of patient-diagnosed, clinician-diagnosed, and even published cases of brown recluse spider bites (or loxoscelism) are incorrect, especially if made in areas where these spiders are not endemic. Many of these lesions are actually due to CA-MRSA.

In addition to arthropod bites, the most common lesions are venomous stings (wasps, hornets, bees, ants, scorpions) or bites (centipedes), furuncle-like lesions due to fly maggots or sand fleas in the skin, and a linear creeping eruption due to a migrating larva.

Clinical Findings

The diagnosis may be difficult when the patient has not noticed the initial attack but suffers a delayed reaction. Individual bites are often in clusters and tend to occur either on exposed parts (eg, midges and gnats) or under clothing, especially around the waist or at flexures (eg, small mites or insects in bedding or clothing). The reaction is often delayed for 1–24 hours or more. Pruritus is almost always present and may be all but intolerable once the patient starts to scratch. Secondary infection may follow scratching. Urticarial wheals are common. Papules may become vesicular. The diagnosis is aided by searching for exposure to arthropods and by considering the patient's occupation and recent activities.

The principal arthropods are as follows:

1. **Fleas:** Fleas are bloodsucking ectoparasites that feed on dogs, cats, humans, and other species. Flea saliva produces papular urticaria in sensitized individuals. To break the life cycle of the flea, one must treat the home and pets, using quick-kill insecticides, residual insecticides, and a growth regulator.
2. **Bedbugs:** In crevices of beds or furniture; bites tend to occur in lines or clusters. Papular urticaria is a characteristic lesion of bedbug (*Cimex lectularius*) bites. Bedbugs are not restricted to any socioeconomic group and are a major health problem in some major metropolitan areas, especially in commercial and residential hotels.
3. **Ticks:** Usually picked up by brushing against low vegetation.

4. **Chiggers or red bugs:** These are larvae of trombiculid mites. A few species confined to particular regions and locally recognized habitats (eg, berry patches, woodland edges, lawns, brush turkey mounds in Australia, poultry farms) attack humans, often around the waist, on the ankles, or in flexures, raising intensely itching erythematous papules after a delay of many hours. The red chiggers may sometimes be seen in the center of papules that have not yet been scratched.
5. **Bird and rodent mites:** Larger than chiggers, bird mites infest birds and their nests. Bites are multiple anywhere on the body. Room air conditioning units may suck in bird mites and infest the inhabitants of the room. Rodent mites from mice or rats may cause similar effects. If the domicile has evidence of rodent activity, then rodent mite dermatitis should be suspected, as the mites are rarely found. Pet rodents or birds may be infested with mites, maintaining the infestation.
6. **Mites in stored products:** These are white and almost invisible and infest products, such as copra, vanilla pods, sugar, straw, cottonseeds, and cereals. Persons who handle these products may be attacked, especially on the hands and forearms and sometimes on the feet.
7. **Caterpillars of moths with urticating hairs:** The hairs are blown from cocoons or carried by emergent moths, causing severe and often seasonally recurrent outbreaks after mass emergence. The gypsy moth is a cause in the eastern United States.
8. **Tungiasis:** Tungiasis is due to the burrowing flea known as *Tunga penetrans* and is found in Africa, the West Indies, and South and Central America. The female burrows under the skin, sucks blood, swells to 0.5 cm, and then ejects her eggs onto the ground. Ulceration, lymphangitis, gangrene, and septicemia may result, in some cases with lethal effect. Simple surgical removal is usually performed.

Prevention

Arthropod infestations are best prevented by avoidance of contaminated areas, personal cleanliness, and disinfection of clothing, bedclothes, and furniture as indicated. Chiggers and mites can be repelled by permethrin applied to the head and clothing. (It is not necessary to remove clothing.) Bedbugs are no longer repelled by permethrin and can survive for up to 1 year without feeding. Aggressive cleaning, usually requiring removal of the affected occupant from the domicile, may be necessary to eradicate bedbug infestation in a residence.

Treatment

Living arthropods should be removed carefully with tweezers after application of alcohol and preserved in alcohol for identification. In endemic Rocky Mountain spotted fever areas, ticks should not be removed with the bare fingers.

Corticosteroid lotions or creams are helpful for the associated pruritus. Topical antibiotics may be applied if secondary infection is suspected. Localized persistent lesions may be treated with intralesional corticosteroids.

Stings produced by many arthropods may be alleviated by applying papain powder (Adolph's Meat Tenderizer) mixed with water, or aluminum chloride hexahydrate (Xerac AC).

Extracts from venom sacs of bees, wasps, yellow jackets, and hornets are available for immunotherapy of patients at risk for anaphylaxis.

Coates SJ et al. Ectoparasites: pediculosis and tungiasis. J Am Acad Dermatol. 2020;82:551. [PMID: 31306729]
Kamath S et al. Infestations, bites, and insect repellents. Pediatr Ann. 2020;49:e124. [PMID: 32155278]
Pace EJ et al. Tickborne diseases: diagnosis and management. Am Fam Physician. 2020;101:530. [PMID: 32352736]
Parola P et al. Bedbugs. N Engl J Med. 2020;382:2230. [PMID: 32492304]

INFLAMMATORY NODULES

ERYTHEMA NODOSUM

ESSENTIALS OF DIAGNOSIS

- Painful nodules without ulceration on anterior aspects of legs.
- Slow regression over several weeks to resemble contusions.
- Women are predominantly affected by a ratio of 10:1 compared to men.
- Some cases associated with infection, IBD, or medication exposure.
- Evaluation for underlying cause is essential.

General Considerations

Erythema nodosum is a symptom complex of panniculitis characterized by tender, erythematous nodules that appear most commonly on the extensor surfaces of the lower legs. It usually lasts about 6 weeks and may recur. Most cases are idiopathic in nature. However, erythema nodosum can be a skin sign of systemic disease. Evaluation and management include making the diagnosis, treating the symptoms, and searching for an underlying cause. The disease may be associated with various infections—streptococcosis, primary coccidioidomycosis, other deep fungal infections, tuberculosis, *Yersinia pseudotuberculosis* and *Y enterocolitica* infection, diverticulitis, or syphilis. It may accompany sarcoidosis, Behçet disease, and IBD. Erythema nodosum may be associated with pregnancy or with use of oral contraceptives. It may occur secondary to medications or, more rarely, an underlying malignancy.

Clinical Findings

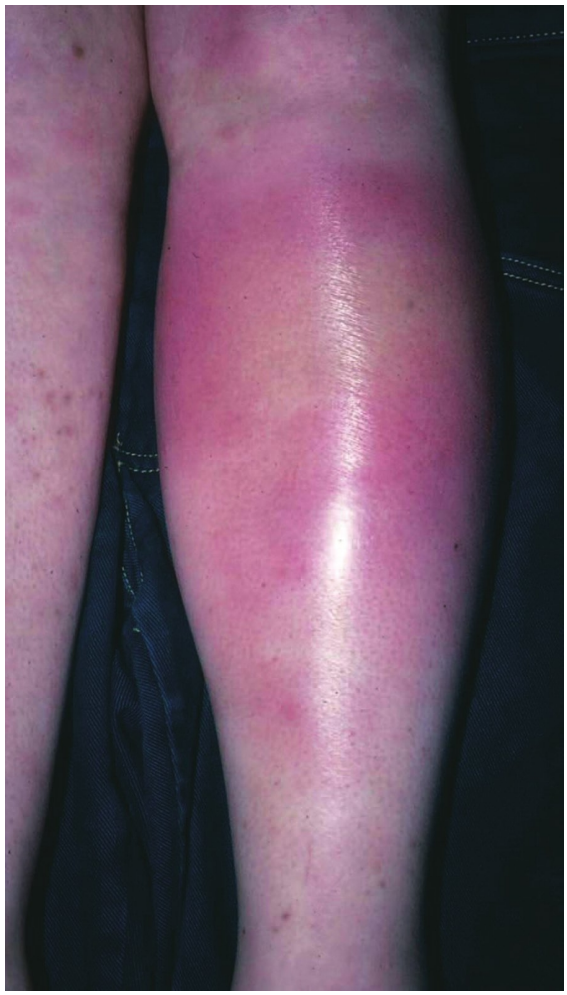
A. Symptoms and Signs

The subcutaneous swellings are exquisitely tender and may be preceded by fever, malaise, and arthralgia. They are

most often located on the anterior surfaces of the legs below the knees but may occur on the arms, trunk, and face. The lesions, 1–10 cm in diameter, are at first pink to red; with regression, all the various hues seen in a contusion can be observed (Figure 6–20) but, as a rule, the lesions do not ulcerate.

B. Laboratory Findings

Evaluation of patients presenting with acute erythema nodosum should include a careful history (including medication exposures) and physical examination. Significant findings include a history of prior upper respiratory infection, diarrheal illness, exposure to tuberculosis, or symptoms of any deep fungal infection endemic to the area. All patients should get a chest radiograph, a purified protein derivative or blood interferon gamma release assay (such as QuantiFERON) (see Pulmonary Tuberculosis in Chapter 9), and two consecutive ASO/DNAse B titers at 2- to 4-week intervals. Coccidioidomycosis should be looked for in patients from endemic areas. If no underlying cause is found, only a small percentage of patients will go on to develop a significant underlying illness (usually sarcoidosis) over the next year.



▲ **Figure 6–20.** Erythema nodosum. (Used, with permission, from TG Berger, MD, Dept Dermatology, UCSF.)

Differential Diagnosis

Unlike other forms of panniculitis, a defining feature of erythema nodosum is that it does not ulcerate. Erythema induratum from tuberculosis is seen on the posterior surfaces of the legs and may ulcerate. Lupus panniculitis presents as tender nodules in fatty areas of the buttocks and posterior arms and heals with depressed scars. In polyarteritis nodosa, the subcutaneous nodules are often associated with fixed livedo reticularis. In its late stages, erythema nodosum must be distinguished from simple bruises and contusions.

Treatment

The underlying cause should be identified and treated. Primary therapy is with NSAIDs in usual doses. Saturated solution of potassium iodide, 5–15 drops three times daily, results in prompt involution in many cases. Complete bed rest may be advisable if the lesions are painful. Systemic therapy directed against the lesions themselves may include corticosteroid therapy (see Chapter 26) (unless contraindicated by associated infection), dapsone, colchicine, or hydroxychloroquine.

Prognosis

The lesions usually disappear after about 6 weeks but may recur.

Pérez-Garza DM et al. Erythema nodosum: a practical approach and diagnostic algorithm. Am J Clin Dermatol. 2021;22:367. [PMID: 33683567]

SCALING DISORDERS

ATOPIC DERMATITIS

ESSENTIALS OF DIAGNOSIS

- Pruritic, xerotic, exudative, or lichenified eruption on face, neck, upper trunk, wrists, and hands and in the antecubital and popliteal folds.
- Personal or family history of atopy (eg, asthma, allergic rhinitis, atopic dermatitis).
- Tendency to recur.
- Onset in childhood most common; onset after age 30 is uncommon.

General Considerations

Atopic dermatitis (also known as eczema) has distinct presentations in people of different ages and races. Diagnostic criteria for atopic dermatitis must include pruritus, typical

morphology and distribution (flexural lichenification, hand eczema, nipple eczema, and eyelid eczema in adults), onset in childhood, and chronicity. Also helpful are (1) a personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis), (2) xerosis-ichthyosis, (3) facial pallor with infraorbital darkening, (4) elevated serum IgE, and (5) repeated skin infections.

Clinical Findings

A. Symptoms and Signs

Itching is a key clinical feature and may be severe and prolonged. Ill-defined, scaly, red plaques affect the face, neck, and upper trunk. The flexural surfaces of elbows and knees are often involved. In chronic cases, the skin is dry and lichenified. In patients with darker skin with severe disease, pigmentation may be lost in lichenified areas. During acute flares, widespread redness with weeping, either diffusely or in discrete plaques, is common. Virtually all patients with atopic dermatitis have skin disease before age 5; therefore, a new diagnosis of atopic dermatitis in an adult over age 30 should be made only after consultation with a dermatologist.

B. Laboratory Findings

Food allergy is an uncommon cause of flares of atopic dermatitis in adults. Eosinophilia and increased serum IgE levels may be present.

Differential Diagnosis

Atopic dermatitis must be distinguished from irritant or allergic contact dermatitis. Seborrheic dermatitis is less pruritic, with frequent scalp and central face involvement, greasy and scaly lesions, and responds quickly to therapy. Psoriasis is marked by sharply demarcated thickly scaled plaques on elbows, knees, scalp, and intergluteal cleft. Secondary staphylococcal or herpetic infections may exacerbate atopic dermatitis and should be considered during hyperacute, weeping flares. An infra-auricular fissure is a cardinal sign of secondary staphylococcal infection.

Treatment

Patient education regarding gentle skin care and proper use of medications is critical to successful management of atopic dermatitis.

A. General Measures

Atopic patients have hyperirritable skin. Anything that dries or irritates the skin may trigger dermatitis. Atopic individuals are sensitive to low humidity and often flare in the winter. Adults with atopic disorders should not bathe more than once daily. Soap should be confined to the armpits, groin, scalp, and feet. Washcloths and brushes should not be used. After rinsing, the skin should be patted dry (not rubbed) and then immediately—within minutes—covered with a thin film of an emollient or a corticosteroid as needed. Plain petrolatum can be used if contact dermatitis resulting from additives in medication is suspected. Skin may be irritated by rough fabrics, including wools and acrylics. Cottons are preferable, but synthetic blends also are tolerated. Other triggers may include sweating, ointments, and heat.

B. Local Treatment

Corticosteroids should be applied sparingly to the dermatitis once or twice daily and rubbed in well. Their potency should be appropriate to the severity of the dermatitis. In general, for treatment of lesions on the body (excluding genitalia, axillary or crural folds), one should begin with triamcinolone 0.1% or a stronger corticosteroid, then taper to hydrocortisone or another slightly stronger mild corticosteroid (alclometasone, desonide). **It is vital that patients taper off corticosteroids and substitute emollients as the dermatitis clears to avoid side effects of corticosteroids**. Tapering is also important to avoid dermatitis flares that may follow abrupt cessation. Tacrolimus ointment (Protopic 0.03% or 0.1%), pimecrolimus cream (Elidel 1%), and crisaborole (Eucrisa 2%) are nonsteroidal topical medications that may be effective in managing atopic dermatitis when applied twice daily. Burning with application occurs in about 50% of patients using Protopic and 10–25% using Elidel but may resolve with continued treatment. These noncorticosteroid medications prevent complications of long-term corticosteroid use, including atrophy or striae. They are safe for application on the face and eyelids but are more expensive than generic topical corticosteroids.

There is a US FDA black box warning for both topical tacrolimus and pimecrolimus due to concerns about the development of T-cell lymphoma. The agents should be used sparingly and only in locations where less expensive corticosteroids cannot be used. They should be avoided in patients at high risk for lymphoma (ie, those with HIV, iatrogenic immunosuppression, or prior lymphoma).

The treatment of atopic dermatitis is dictated by the pattern of the dermatitis—acute/weepy, subacute/scaly, or chronic/lichenified.

1. Acute weeping lesions—Staphylococcal or herpetic superinfection should be excluded by bacterial or viral culture, or both. Use water or aluminum subacetate solution (Domeboro or burow solution), or colloidal oatmeal as a bath or as wet dressings for 10–30 minutes two to four times daily. Lesions on extremities may be bandaged for protection at night. Use high-potency corticosteroids after soaking but spare the face and body folds. Tacrolimus is usually not tolerated at this stage. Systemic corticosteroids may be required. An allergic or irritating contactant should also be considered when acute weeping lesions are present, since contact dermatitis is more likely to develop in atopic patients.

2. Subacute or scaly lesions—The lesions are dry but still red and pruritic. Mid- to high-potency corticosteroids in ointment form should be continued until skin lesions are cleared and itching is decreased substantially. At that point, patients should begin a 2- to 4-week taper from twice-daily to daily dosing with topical corticosteroids to reliance on emollients, with occasional use of corticosteroids only to

inflamed areas. It is preferable to switch to daily use of a low-potency corticosteroid instead of further tapering the frequency of usage of a more potent corticosteroid. Tacrolimus and pimecrolimus may be substituted if corticosteroids cannot be stopped completely.

3. Chronic, dry, lichenified lesions—Thickened and usually well demarcated, they are best treated with high-potency to ultra–high-potency corticosteroid ointments. Nightly occlusion for 2–6 weeks may enhance the initial response. Adding tar preparations, such as liquor carbonis detergens 10% in Aquaphor or 2% crude coal tar may be beneficial.

4. Maintenance treatment—Once symptoms have improved, constant application of effective moisturizers is recommended to prevent flares. In patients with moderate disease, use of topical anti-inflammatories only on weekends or three times weekly can prevent flares.

C. Systemic and Adjuvant Therapy

Systemic corticosteroids are indicated only for severe acute exacerbations. Oral prednisone dosages should be high enough to suppress the dermatitis quickly, usually starting with 1 mg/kg daily. The dosage is then tapered off over a period of 2–4 weeks. Owing to the chronic nature of atopic dermatitis and the side effects of long-term systemic corticosteroids, **ongoing use of these agents is not recommended for maintenance therapy.** Bedtime doses of hydroxyzine, diphenhydramine, or doxepin may be helpful via their sedative properties to mitigate perceived pruritus. Dupilumab is a targeted immunomodulator with minimal systemic adverse effects and requires minimal laboratory monitoring. Janus kinase (JAK) inhibitors (upadacitinib, abrocitinib), cyclosporine, mycophenolate mofetil, methotrexate, or azathioprine may also be used for the most severe and recalcitrant cases.

Complications of Treatment

The clinician should monitor for skin atrophy. Fissures, crusts, erosions, or pustules may indicate staphylococcal or herpetic infection clinically. Eczema herpeticum (herpes simplex superinfection) is manifested by monomorphic vesicles, crusts, or scalloped erosions superimposed on atopic dermatitis or other extensive eczematous processes and is treated with oral or intravenous acyclovir. Systemic antistaphylococcal antibiotics—such as a first-generation cephalosporin or doxycycline if methicillin-resistant *Staphylococcus aureus* is suspected—should be given only if indicated and guided by bacterial culture. Cultures to exclude methicillin-resistant *S aureus* are recommended. In this setting, continuing and augmenting the topical anti-inflammatory treatment often improves the dermatitis despite the presence of infection.

Prognosis

Atopic dermatitis runs a chronic or intermittent course. Affected adults may have only hand dermatitis. Prognostic factors for persistence into adulthood include generalized disease or onset early in childhood and asthma. Only 40–60% of these patients have lasting remissions.

Drucker AM et al. Systemic immunomodulatory treatments for patients with atopic dermatitis: a systematic review and network meta-analysis. JAMA Dermatol. 2020;156:659. [PMID: 32320001]
Lam M et al. Association between topical calcineurin inhibitor use and risk of cancer, including lymphoma, keratinocyte carcinoma, and melanoma: a systematic review and meta-analysis. JAMA Dermatol. 2021;157:549. [PMID: 33787818]
Langan SM et al. Atopic dermatitis. Lancet 2020;396:345. [PMID: 32738956]

LICHEN SIMPLEX CHRONICUS (Circumscribed Neurodermatitis)

ESSENTIALS OF DIAGNOSIS

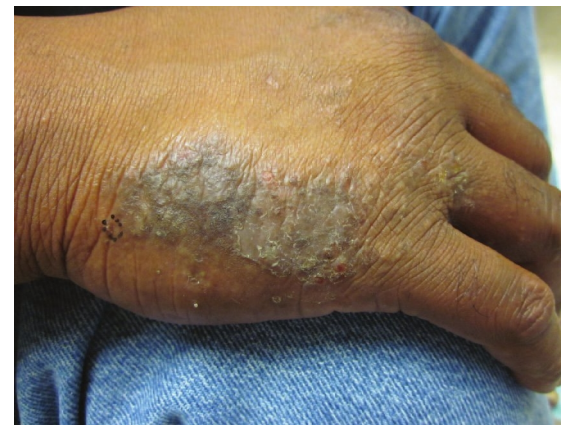
- Chronic itching and scratching.
- Lichenified lesions with exaggerated skin lines overlying a thickened, well-circumscribed, scaly plaque.
- Predilection for nape of neck, wrists, external surfaces of forearms, lower legs, and genitals.

General Considerations

Lichen simplex chronicus represents a self-perpetuating scratch-itch cycle that is hard to disrupt.

Clinical Findings

Intermittent itching incites the patient to scratch the lesions and may interfere with sleep. Dry, hypertrophic, lichenified plaques appear on the neck, wrists, ankles, or perineum (Figure 6–21). The patches are rectangular, thickened, and hyperpigmented. The skin lines are exaggerated.



▲ **Figure 6–21.** Lichen simplex chronicus on the hand. (Used, with permission, from Lindy Fox, MD.)

Differential Diagnosis

This disorder can be differentiated from plaque-like lesions such as psoriasis (redder lesions having whiter scales on the elbows, knees, and scalp and nail findings), lichen planus (violaceous, usually smaller polygonal papules), and nummular (coin-shaped) dermatitis. Lichen simplex chronicus may complicate chronic atopic dermatitis or scabetic infestation.

Treatment

For lesions in extragenital regions, ultra-high potency topical corticosteroids are effective, with or without occlusion, when used twice daily for several weeks (Table 6–2). In some patients, flurandrenolide (Cordran) tape may be effective, since it prevents scratching and rubbing of the lesion. The injection of triamcinolone acetonide suspension (5–10 mg/mL) into the lesions may occasionally be curative. Continuous occlusion with a flexible hydrocolloid dressing for 7 days at a time for 1–2 months may also be helpful. Dupilumab is a new treatment option for generalized disease or prurigo nodularis, its related condition. For genital lesions, see the section Pruritus Ani.

Prognosis

The disease tends to remit during treatment but may recur or develop at another site.

Calugareanu A et al; French Group of Research and Study in Atopic Dermatitis (Groupe de Recherche sur l'Eczéma Atopique, GREAT) from the French Society of Dermatology (SFD). Effectiveness and safety of dupilumab for the treatment of prurigo nodularis in a French multicenter adult cohort of 16 patients. J Eur Acad Dermatol Venereol. 2020;34:e74. [PMID: 31529718]

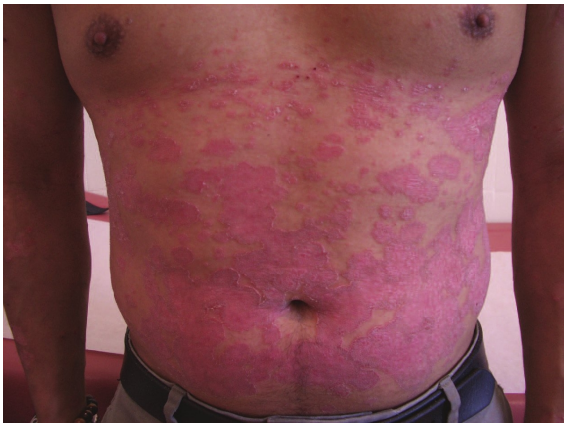
PSORIASIS

ESSENTIALS OF DIAGNOSIS

- Silvery scales on bright red, well-demarcated plaques, usually on the knees, elbows, and scalp.
- Nails: pitting and onycholysis (separation of the nail plate from the bed).
- Mild itching is common.
- May be associated with psoriatic arthritis.
- Histopathology helpful.

General Considerations

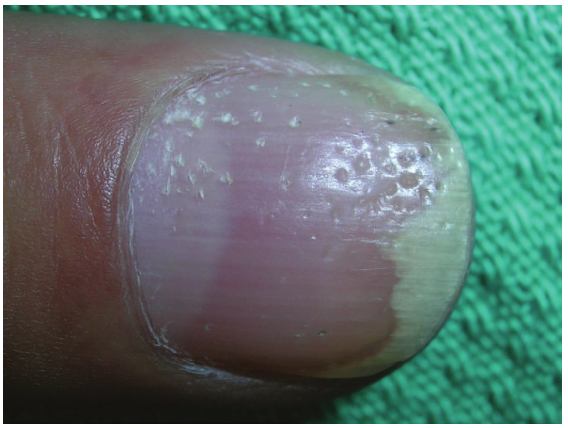
Psoriasis is a common benign, chronic inflammatory skin disease with both a genetic basis and known environmental triggers. Injury or irritation of normal skin tends to induce lesions of psoriasis at the site (Koebner phenomenon). Obesity worsens psoriasis, and significant weight loss may lead to substantial improvement. Psoriasis has several variants—the most common is the plaque type and hand involvement is also common. Eruptive (guttate) psoriasis consisting of numerous, smaller lesions 3–10 mm in diameter occurs occasionally after streptococcal pharyngitis. Rarely, life-threatening forms (generalized pustular and erythrodermic psoriasis) may occur.



▲ **Figure 6–22.** Extensive plaque psoriasis involving trunk of person with dark skin type. (Used, with permission, from Kanade Shinkai, MD.)

Clinical Findings

There are often no symptoms, but itching may occur and be severe. Favored sites include the scalp, elbows, knees, palms and soles, and nails. The lesions are red, sharply defined plaques covered with silvery scale (Figure 6–22). The glans penis and vulva may be affected. Occasionally, only the flexures (axillae, inguinal areas) are involved (termed inverse psoriasis). Fine stippling ("pitting") in the nails is highly suggestive of psoriasis (Figure 6–23) as is onycholysis. The combination of red plaques with silvery scales on elbows and knees, with scaliness in the scalp or



▲ **Figure 6–23.** Nail pitting due to psoriasis in a patient with dark skin. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

nail findings, is diagnostic. Patients with psoriasis often have a pink or red intergluteal fold. Not all patients have findings in all locations. Some patients have mainly hand or foot dermatitis with minimal findings elsewhere. There may be associated arthritis that is most commonly distal and oligoarticular, although the rheumatoid variety with a negative rheumatoid factor may occur. The psychosocial impact of psoriasis is a major factor in determining the treatment of the patient.

Differential Diagnosis

Psoriasis lesions are well demarcated and affect extensor surfaces—in contrast to atopic dermatitis, with poorly demarcated plaques in flexural distribution. In body folds, scraping and culture for *Candida* and examination of scalp and nails will distinguish inverse psoriasis from intertrigo and candidiasis. Dystrophic changes in nails may mimic onychomycosis, and a potassium hydroxide (KOH) preparation or fungal culture is valuable in diagnosis. The cutaneous features of reactive arthritis, pityriasis rosea, SLE, and syphilis mimic psoriasis.

Treatment

There are many therapeutic options in psoriasis to be chosen according to the extent (body surface area [BSA] affected) and the presence of other findings (for example, arthritis). Certain medications, such as beta-blockers, antimalarials, statins, lithium, and prednisone taper may flare or worsen psoriasis. Patients with moderate to severe psoriasis should be managed by or in conjunction with a dermatologist.

A. Limited Disease

For patients with large plaques and less than 10% of the BSA involved, the easiest regimen is to use a high-potency to ultra–high-potency topical corticosteroid cream or ointment. It is best to restrict the ultra–high-potency corticosteroids to 2–3 weeks of twice-daily use and then use them in a pulse fashion three or four times on weekends or switch to a mid-potency corticosteroid. Topical corticosteroids rarely induce a lasting remission. Initially, patients may be treated with twice-daily topical corticosteroids plus a vitamin D analog (calcipotriene ointment 0.005% or calcitriol ointment 0.003%) twice daily. This rapidly clears the lesions; eventually, the topical corticosteroids are stopped, and once- or twice-daily application of the vitamin D analog is continued long-term. Calcipotriene usually cannot be applied to the groin or face because of irritation. Treatment of extensive psoriasis with vitamin D analogs may result in hypercalcemia, so that the maximum dose for calcipotriene is 100 g/week and for calcitriol it is 200 g/week. Calcipotriene is incompatible with many topical corticosteroids (but not halobetasol), so if used concurrently, it must be applied at a different time. For patients with numerous small papules and plaques, such as guttate psoriasis, phototherapy is the best therapy.

For thick plaques on the scalp, start with a tar shampoo, used daily if possible. Additional treatments include 6% salicylic acid gel (eg, Keralyt), P & S solution (phenol, mineral oil, and glycerin), or fluocinolone acetonide 0.01% in oil (Derma-Smoothe/FS) under a shower cap at night, and shampoo in the morning. In order of increasing potency, triamcinolone 0.1%, fluocinolone, betamethasone dipropionate, amcinonide, and clobetasol are available in solution form for use on the scalp twice daily. Tacrolimus ointment 0.1% or 0.03% or pimecrolimus cream 1% may be effective in intertriginous, genital, and facial psoriasis, where potent corticosteroids are not recommended due to skin atrophy.

B. Moderate Disease

Psoriasis affecting 10–30% of the patient's BSA is frequently treated with UV phototherapy, either in a medical office or via a home light unit. Systemic agents listed below may also be used.

C. Moderate to Severe Disease

If psoriasis in a given location is severe or involves more than 30% of the body surface, it is difficult to treat with topical agents. These patients may be best managed in partnership with a dermatologist, especially when considering systemic therapy. The treatment of choice is outpatient narrowband UVB (NB-UVB) three times weekly. Clearing occurs in an average of 7 weeks, and maintenance may be required. Psoriatic arthritis may require distinct treatments, and benefits from management in partnership with a rheumatologist or dermatologist.

Methotrexate is effective for severe psoriasis in doses up to 25 mg once weekly according to published protocols. Long-term methotrexate use may be associated with cirrhosis. After receiving a 3.5–4-g cumulative dose, the patient should be referred to a hepatologist for evaluation. Administration of folic acid, 1–2 mg daily, can eliminate nausea caused by methotrexate without compromising efficacy.

Acitretin, a synthetic retinoid, is most effective for pustular psoriasis in oral dosages of 0.5–0.75 mg/kg/day. Liver enzymes and serum lipids must be checked periodically. Because acitretin is a teratogen and persists for 2–3 years in fat, women of childbearing age must wait at least 3 years after completing acitretin treatment before considering pregnancy. When used as single agents, retinoids will flatten psoriatic plaques, but will rarely result in complete clearing. Retinoids find their greatest use when combined with phototherapy—either UVB or PUVA, with which they are synergistic.

Cyclosporine dramatically improves psoriasis and may be used to control severe cases. Rapid relapse (rebound) frequently occurs after cessation of therapy, so another agent must be added if cyclosporine is stopped. The tumor necrosis factor (TNF) inhibitors etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira) are effective in pustular and chronic plaque psoriasis and are also effective for the associated arthritis. Infliximab provides the most rapid response and can be used for severe pustular or erythrodermic flares. Etanercept is used more frequently for long-term treatment at a dose of 50 mg subcutaneously twice weekly for 3 months, then 50 mg

once weekly. All three TNF inhibitors can also induce or worsen psoriasis. IL-12/23 monoclonal antibodies (ustekinumab [Stelara], guselkumab, risankizumab), JAK inhibitors (tofacitinib, approved for use in rheumatoid arthritis but with strong data supporting its use in psoriasis), and IL-17 monoclonal antibodies (secukinumab, brodalumab, and ixekizumab) may be the most effective treatments among biologics. The oral phosphodiesterase 4 inhibitor apremilast is an approved option for plaque-type psoriasis and psoriatic arthritis with minimal immunosuppressive effects and requires no laboratory monitoring.

Prognosis

The course of psoriasis may be chronic and unpredictable, and it may be refractory to treatment. Patients (especially those older than 40 years) should be monitored for metabolic syndrome, which correlates with the severity of their skin disease. Complications of systemic therapy occur and active monitoring for infection is needed.

Armstrong AW et al. Comparison of biologics and oral treatments for plaque psoriasis: a meta-analysis. JAMA Dermatol. 2020;156:256. [PMID: 32022825]
Armstrong AW et al. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. JAMA. 2020;323:1945. [PMID: 32427307]
Sbidian E et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Update in: Cochrane Database Syst Rev. 2021;4:CD011535. [PMID: 31917873]

PITYRIASIS ROSEA

ESSENTIALS OF DIAGNOSIS

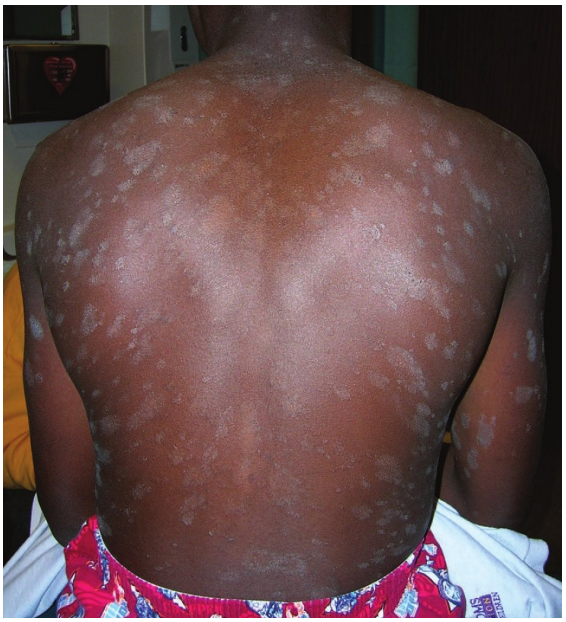
- Oval, fawn-colored, scaly eruption following cleavage lines of trunk.
- Herald patch precedes eruption by 1–2 weeks.
- Occasional pruritus.

General Considerations

Pityriasis rosea is a common mild, acute inflammatory disease that is 50% more common in females. Young adults are principally affected, mostly in the spring or fall. Concurrent household cases have been reported.

Clinical Findings

Itching is common but usually mild. The diagnosis is made by finding one or more classic lesions, such as oval, fawn-colored plaques up to 2 cm in diameter. The centers of a few lesions may have a characteristic crinkled or "cigarette paper" appearance and a collarette scale, ie, a thin bit of scale that is bound at the periphery and free in the center. Lesions follow cleavage lines on the trunk (so-called Christmas tree pattern, Figure 6–24), and the proximal portions of the extremities are often involved. A variant that affects the flexures (axillae and groin), so-called inverse pityriasis rosea, and a papular variant, especially in patients with more darkly pigmented skin types, also occur. An initial lesion ("herald patch") that is often larger than the later lesions often precedes the general eruption by 1–2 weeks. The eruption usually lasts 6–8 weeks and heals without scarring.



▲ **Figure 6–24.** Pityriasis rosea with scaling lesions following skin lines and resembling a Christmas tree. (Used, with permission, from EJ Mayeaux, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

Differential Diagnosis

Serologic testing for syphilis should be performed if clinical risk factors are present. Palmar and plantar or mucous membrane lesions or adenopathy are features suggestive of secondary syphilis. Tinea corporis may present with a few red, slightly scaly plaques. Typically, the number of plaques of tinea corporis are significantly fewer than the number seen in pityriasis rosea. A potassium hydroxide examination should be performed to exclude a fungal cause. Seborrheic dermatitis on occasion presents on the body with poorly demarcated patches over the sternum, in the pubic area, and in the axillae. Tinea versicolor lacks the typical collarette rimmed lesions. Guttate or plaque psoriasis is an important diagnostic consideration and biopsy can help differentiate these from pityriasis rosea. Certain medications and immunizations rarely may induce a skin eruption mimicking pityriasis rosea. A pityriasis rosea–like eruption has been reported in association with SARS-CoV2 infection and COVID-19 vaccination.

Treatment

Pityriasis rosea often requires no treatment unless patients are symptomatic. In darker-skinned individuals, more

aggressive management may be indicated because dyspigmentation of lesions may result. While well-designed clinical trials have not demonstrated highly effective treatments, most dermatologists recommend UVB treatments or a short course of prednisone for severe or severely symptomatic cases. For mild to moderate cases, topical corticosteroids of medium strength (triamcinolone 0.1%) and oral antihistamines may be used if pruritus is bothersome. The role of macrolide antibiotics is not evidence based.

Prognosis

Pityriasis rosea is usually an acute self-limiting illness that typically disappears in about 6 weeks, although prolonged variants have been reported.

Cohen L et al. Dermatologic problems commonly seen by the allergist/immunologist. J Allergy Clin Immunol Pract. 2020;8:102. [PMID: 31351991]
Freeman EE et al. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. J Am Acad Dermatol.2020;83:1118. [PMID: 32622888]
Schwartzberg L et al. Cutaneous manifestations of COVID-19. Cutis. 2021;107:90. [PMID: 33891838]

SEBORRHEIC DERMATITIS

ESSENTIALS OF DIAGNOSIS

- Dry scales and underlying erythema.
- Scalp, central face, presternal, interscapular areas, umbilicus, and body folds.

General Considerations

Seborrheic dermatitis is an acute or chronic papulosquamous dermatitis that often coexists with psoriasis and is associated with inflammation due to *Malassezia* species.

Clinical Findings

The scalp, face, chest, back, umbilicus, eyelid margins, genitalia, and body folds have dry scales (dandruff) or oily yellowish scurf (Figure 6–25). Pruritus is a variable finding. Patients with Parkinson disease, HIV-infected patients, and patients who become acutely ill often have seborrheic dermatitis.

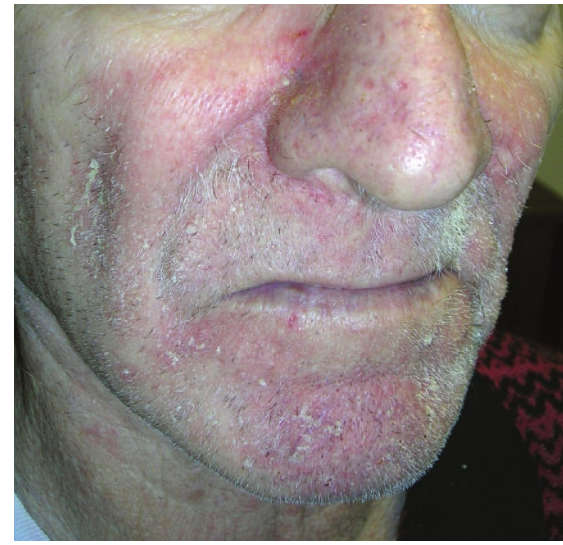
Differential Diagnosis

There is a spectrum from seborrheic dermatitis to scalp psoriasis. Extensive seborrheic dermatitis may simulate intertrigo in flexural areas, but scalp, face, and sternal involvement suggests seborrheic dermatitis.

Treatment

A. Seborrhea of the Scalp

Shampoos that contain zinc pyrithione or selenium are used daily if possible. These may be alternated with ketoconazole shampoo (1% or 2%) used twice weekly. A combination of shampoos is used in refractory cases. Tar shampoos are also effective for milder cases and for scalp psoriasis. Topical corticosteroid solutions or lotions are then added if necessary and are used twice daily. (See treatment for scalp psoriasis, above.)



▲ **Figure 6–25.** Close-up of seborrheic dermatitis showing flaking skin and erythema around the beard region. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

B. Facial Seborrheic Dermatitis

The mainstay of therapy is a mild corticosteroid (hydrocortisone 1%, alclometasone, desonide) used intermittently and not near the eyes. If the disorder cannot be controlled with intermittent use of a mild topical corticosteroid alone, ketoconazole 2% cream is added twice daily. Topical tacrolimus and pimecrolimus are steroid-sparing alternatives and may be more effective than antifungal therapy.

C. Seborrheic Dermatitis of Nonhairy or Intertriginous Areas

Low-potency corticosteroid creams—ie, 1% or 2.5% hydrocortisone, desonide, or alclometasone dipropionate—are highly effective when applied twice daily for 5–7 days and then once or twice weekly for maintenance as necessary. Selenium lotion, ketoconazole, or clotrimazole gel or cream may be a useful adjunct. Tacrolimus or pimecrolimus topically may avoid corticosteroid atrophy in chronic cases.

D. Involvement of Eyelid Margins

"Marginal blepharitis" usually responds to gentle cleaning of the lid margins nightly as needed, with undiluted baby shampoo or eyelid cleanser using a cotton swab.

Prognosis

The tendency is for lifelong recurrences. Individual outbreaks may last weeks, months, or years.

Joly P et al. Tacrolimus 0.1% versus ciclopiroxolamine 1% for maintenance therapy in patients with severe facial seborrheic dermatitis: a multicenter, double-blind, randomized controlled study. J Am Acad Dermatol. 2021;84:1278. [PMID: 33010323]
Piquero-Casals J et al. Non-steroidal topical therapy for facial seborrheic dermatitis. J Drugs Dermatol. 2020;19:658. [PMID: 32574015]

LICHEN PLANUS

ESSENTIALS OF DIAGNOSIS

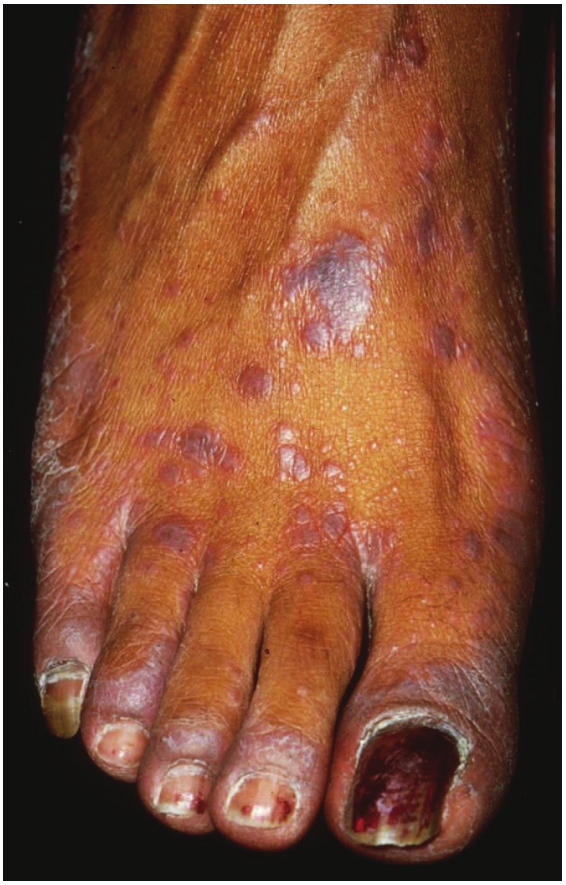
- Pruritic, violaceous, flat-topped papules with fine white streaks and symmetric distribution.
- Lacy or erosive lesions of the buccal, vulvar, and vaginal mucosa; nail dystrophy.
- Commonly seen along linear scratch marks (Koebner phenomenon) on anterior wrists, penis, and legs.
- Diagnostic histopathology.

General Considerations

Lichen planus is an inflammatory pruritic disease of the skin and mucous membranes characterized by distinctive papules with a predilection for the flexor surfaces and trunk. The three cardinal findings are typical skin lesions, mucosal lesions, and histopathologic features of band-like infiltration of lymphocytes in the upper dermis. Lichenoid drug eruptions can resemble lichen planus clinically and histologically. The most common medications include sulfonamides, tetracyclines, quinidine, NSAIDs, beta-blockers, and hydrochlorothiazide. Hepatitis C infection is found with greater frequency in lichen planus patients than in controls. Allergy to mercury and other metal-containing amalgams can trigger oral lesions identical to lichen planus.

Clinical Findings

The lesions are violaceous, flat-topped, angulated papules, up to 1 cm in diameter, discrete or in clusters (Figure 6–26), with very fine white streaks (Wickham striae) on the flexor surfaces of the wrists and ankles; on lower back; and on mucous membranes, including the penis, lips, tongue, buccal, vulvar, vaginal, esophageal, and anorectal mucosa. Itching is mild to severe. The papules may become bullous or eroded. The disease may be generalized. Mucous membrane lesions have a lacy white network overlying them that may be confused with leukoplakia. The presence of oral and vulvovaginal lichen planus in the same patient is common. Patients with both these mucous membranes involved are at much higher risk for esophageal lichen planus. Lichen planus is also a cause of alopecia and nail dystrophy. The Koebner phenomenon (appearance of lesions in areas of trauma) may be seen.



▲ **Figure 6–26. Lichen planus.** (Used, with permission, from TG Berger, MD, Dept Dermatology, UCSF.)

A special form of lichen planus is the erosive or ulcerative variety, a major problem in the mouth or genitalia. Squamous cell carcinoma develops in up to 5% of patients with erosive oral or genital lichen planus and may occur in esophageal lichen planus. There is also an increased risk of squamous cell carcinoma developing in lesions of hypertrophic lichen planus on the lower extremities.

Differential Diagnosis

Lichen planus must be distinguished from similar lesions produced by medications and other papular lesions, such as psoriasis, lichen simplex chronicus, graft-versus-host disease, and syphilis. Lichen planus on the mucous membranes must be differentiated from leukoplakia. Erosive oral lesions require biopsy and often direct immunofluorescence for diagnosis since lichen planus may simulate other erosive diseases, especially autoimmune blistering diseases that involve the oral mucosa.

Treatment

A. Topical Therapy

Superpotent topical corticosteroids applied twice daily are most helpful for localized disease in nonflexural areas.

Alternatively, high-potency corticosteroid cream or ointment may be used nightly under thin, pliable plastic film.

Topical tacrolimus appears effective in oral and vaginal erosive lichen planus, but long-term therapy is required to prevent relapse. If tacrolimus is used, lesions must be observed carefully for development of squamous cell carcinoma. Since absorption can occur through mucous membranes, serum tacrolimus levels should be checked at least once if widespread mucosal application (more than 5–10 cm^2) is used. If the erosive oral lichen planus lesions are adjacent to a metal-containing amalgam, removal of the amalgam may result in clearing of the erosions.

B. Systemic Therapy

NB-UVB, bath PUVA, oral PUVA, and the combination of an oral retinoid plus PUVA (re-PUVA) are all forms of phototherapy that can improve lichen planus. Hydroxychloroquine (5 mg/kg once daily), acitretin (10–25 mg orally daily), cyclosporine (3–5 mg/kg orally), and mycophenolate mofetil (1 g orally twice daily) can also be effective in mucosal and cutaneous lichen planus. Apremilast, 30 mg twice daily, has reported efficacy in case series. JAK inhibitors and anti-IL-12/23 and anti-IL-17 agents have also been used with success in refractory cases. Corticosteroids may be required in severe cases or in circumstances where the most rapid response to treatment is desired. Unfortunately, relapse almost always occurs as the corticosteroids are tapered, making systemic corticosteroid therapy an impractical option for the management of chronic lichen planus.

Prognosis

Lichen planus is a benign disease, but it may persist for months or years and may be recurrent. Hypertrophic lichen planus and oral lesions tend to be especially persistent, and neoplastic degeneration has been described in chronically eroded lesions.

Boch K et al. Lichen planus. Front Med (Lausanne). 2021;8:737813. [PMID: 34790675]

Li C et al. Global prevalence and incidence estimates of oral lichen planus: a systematic review and meta-analysis. JAMA Dermatol. 2020;156:172. [PMID: 31895418]

CUTANEOUS LUPUS ERYTHEMATOSUS

ESSENTIALS OF DIAGNOSIS

- Localized violaceous red plaques, usually on the head (discoid lupus erythematosus) or the trunk (chronic cutaneous lupus erythematosus).
- Scaling, follicular plugging, atrophy, dyspigmentation, and telangiectasia of involved areas.
- Photosensitivity.
- Distinctive histology.

General Considerations

Common forms of cutaneous lupus include chronic cutaneous lupus erythematosus (CCLE), typically chronic scarring (discoid) lupus erythematosus (DLE), and erythematous nonscarring red plaques of subacute cutaneous lupus erythematosus (SCLE). All occur most frequently in photoexposed areas. Permanent hair loss and loss of pigmentation are common sequelae of discoid lesions. SLE is discussed in Chapter 20. Patients with SLE may have DLE or SCLE lesions.

Clinical Findings

A. Symptoms and Signs

Symptoms are usually mild. In DLE, the lesions consist of violaceous red, well-localized, single or multiple plaques, 5–20 mm in diameter, usually on the face, scalp, and external ears (conchal bowl). In discoid lesions, there is atrophy, telangiectasia, central depigmentation or scarring, a hyperpigmented rim, and follicular plugging. On the scalp, significant permanent hair loss may occur. In SCLE, the lesions are erythematous annular or psoriasiform plaques up to several centimeters in diameter and favor the upper chest and back.

B. Laboratory Findings

In patients with DLE, SLE should be considered if the following findings are present: positive antinuclear antibody (ANA), other positive serologic studies (eg, anti-double-stranded DNA or anti-Smith antibody), high ESR, proteinuria, hypocomplementemia, widespread lesions (not localized to the head), nail fold changes (dilated or thrombosed nail fold capillary loops), or arthralgias with or without arthritis. Patients with marked photosensitivity and symptoms otherwise suggestive of lupus may have negative ANA tests but are positive for antibodies against Ro/SSA or La/SSB (SCLE).

Differential Diagnosis

The diagnosis is based on the clinical appearance confirmed by skin biopsy in all cases. In DLE, the scale is dry and "thumbtack-like" and thus distinguished from that of seborrheic dermatitis and psoriasis. Older lesions have hyperpigmented borders, depigmented central scarring, or areas of hair loss that also differentiate lupus from these diseases. Ten percent of patients with SLE have discoid skin lesions, and 5% of patients with discoid lesions have SLE. A number of medications may induce SCLE with a positive Ro/SSA.

Treatment

A. General Measures

Use photoprotective clothing and broad-spectrum sunblock of SPF of 30 or more daily. UVA coverage is essential in photosensitive patients. Avoid radiation therapy or medications that are potentially photosensitizing when possible.

B. Local Treatment

For limited lesions, the following should be tried before systemic therapy: high-potency corticosteroid creams applied each night and covered with airtight, thin, pliable plastic film (eg, Saran Wrap); Cordran tape; or ultra–high-potency corticosteroid cream or ointment applied twice daily without occlusion.

C. Local Infiltration

Triamcinolone acetonide suspension, 2.5–10 mg/mL, may be injected into DLE lesions once a month.

D. Systemic Treatment

1. Antimalarials—These medications should be used only when the diagnosis is secure because they have been associated with flares of psoriasis, which may be in the differential diagnosis.

A. Hydroxychloroquine sulfate—Daily dose of no more than 5 mg/kg orally (real-weight) for several months may be effective and is often used prior to chloroquine. A minimum 3-month trial is recommended. Screening for ocular toxicity is needed.

B. Chloroquine sulfate—250 mg orally daily may be effective in some cases when hydroxychloroquine is not.

2. Isotretinoin—Isotretinoin, 1 mg/kg/day orally, is effective in hypertrophic DLE lesions.

3. Thalidomide—Thalidomide is effective in refractory cases in doses of 50–300 mg orally daily. Monitor for neuropathy. Lenalidomide (5–10 mg orally daily) may also be effective with less risk for neuropathy.

Isotretinoin, thalidomide, and lenalidomide are teratogens and should be used with appropriate contraception and monitoring in women of childbearing age.

Prognosis

The disease is persistent but not life-endangering unless systemic lupus is present. Treatment with one or more antimalarials is effective in more than half of cases. Patients with cutaneous lupus erythematosus should be examined and tested annually (CBC and UA) to screen for early signs of systemic involvement. Although the only morbidity may be cosmetic, this can have significant quality of life impact in more darkly pigmented patients with widespread disease. Scarring alopecia can be prevented or lessened with close attention and aggressive therapy. Over years, DLE tends to become inactive. Drug-induced SCLE usually resolves over months when the inciting medication is stopped.

Fairley JL et al. Management of cutaneous manifestations of lupus erythematosus: a systematic review. Semin Arthritis Rheum. 2020;50:95. [PMID: 31526594]

Shi H et al. Treatment of cutaneous lupus erythematosus: current approaches and future strategies. Curr Opin Rheumatol. 2020;32:208. [PMID: 32141953]

VESICULAR & BLISTERING DERMATOSES

CONTACT DERMATITIS

ESSENTIALS OF DIAGNOSIS

- Erythema and edema, with pruritus, vesicles, bullae, weeping, or crusting.
- **Irritant contact dermatitis:** occurs only in area of direct contact with irritant.
- **Allergic contact dermatitis:** extends beyond area of direct contact with allergen; positive patch test.

General Considerations

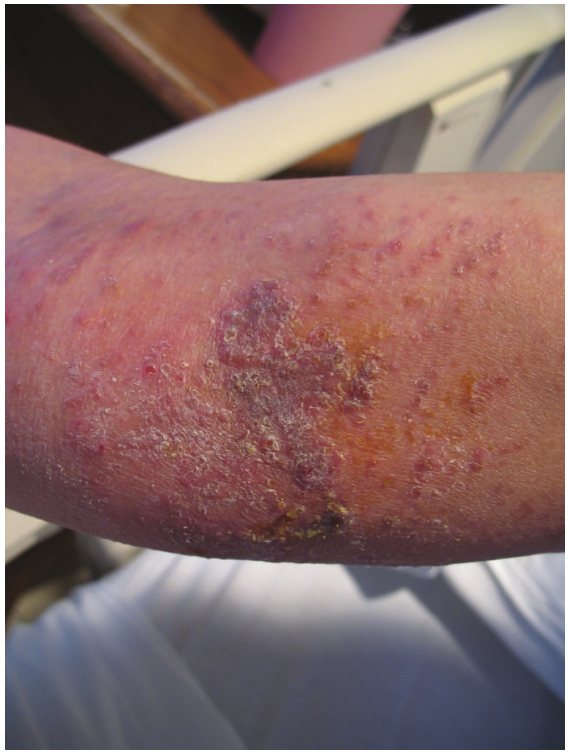
Contact dermatitis (irritant or allergic) is an acute or chronic dermatitis that results from direct skin contact with chemicals or allergens. Eighty percent of cases are due to excessive exposure to or additive effects of universal irritants (eg, soaps, detergents, organic solvents) and are called **irritant contact dermatitis**. The most common causes of **allergic contact dermatitis** are poison ivy or poison oak, topically applied antimicrobials (especially bacitracin and neomycin), anesthetics (benzocaine), preservatives, jewelry (nickel), rubber, essential oils, propolis (from bees), vitamin E, and adhesive tape. Occupational exposure is an important cause of allergic contact dermatitis.

Clinical Findings

A. Symptoms and Signs

1. Allergic contact dermatitis—The acute phase is characterized by intense pruritus, tiny vesicles, and weepy and crusted lesions (Figure 6–27). The lesions, distributed on exposed parts or in unusual asymmetric patterns, consist of erythematous macules, papules, and vesicles and may occur beyond the contact area, distinguishing it from irritant dermatitis. The affected area may also be edematous and warm with honey-colored crusting, simulating—and at times complicated by—bacterial or viral infection. The pattern of the eruption may be diagnostic (eg, typical linear streaked vesicles on the extremities in poison oak or ivy dermatitis). The location will often suggest the cause: scalp involvement suggests hair dyes or shampoos; face involvement suggests creams, cosmetics, soaps, shaving materials, nail polish; and neck involvement suggests jewelry, hair dyes. Reactions may not develop for 48–72 hours after exposure.

2. Irritant contact dermatitis—The rash is erythematous and scaly (but less likely vesicular) and occurs only in the direct sites of contact with the irritant. Resolving or chronic contact dermatitis presents with scaling, erythema, and possibly thickened skin. Itching, burning, and stinging may be severe in both allergic and irritant contact



▲ **Figure 6–27.** Allergic contact dermatitis to an adhesive dressing in patient with darker skin. Key features are erythematous papules with impetigo-like honey-colored crusting. (Used, with permission, from Kanade Shinkai, MD.)

dermatitis. Reactions may develop within 24 hours of contact exposure.

B. Laboratory Findings

Gram stain and culture will rule out impetigo or secondary infection (impetiginization). After the episode of allergic contact dermatitis has cleared, patch testing may be useful if the triggering allergen is not known.

Differential Diagnosis

Asymmetric distribution, blotchy erythema around the face, linear lesions, and a history of exposure help distinguish acute contact dermatitis from other skin lesions. The most commonly mistaken diagnosis is impetigo, herpetic infection, or cellulitis. Chronic allergic contact dermatitis must be differentiated from scabies, particularly if itching is generalized; atopic dermatitis; and pompholyx.

Prevention

Removal of the causative oil by washing with liquid soap may be effective if done within 30 minutes after exposure to poison oak or ivy. Goop (oil remover) and Tecnu (chemical inactivator) are also effective but more expensive without increased efficacy. Over-the-counter barrier creams may be effective when applied prior to exposure and prevent/reduce the severity of the dermatitis.

The mainstay of prevention is identification of the agent causing the dermatitis and strict avoidance of exposure or use of protective clothing and gloves. Some allergens will transmit through latex gloves. In industry-related cases, prevention may require special accommodations or retraining the worker.

Treatment

A. Overview

Localized involvement (except on the face) can often be managed solely with topical agents. While local measures are important, severe or widespread involvement is difficult to manage without systemic corticosteroids because even the highest-potency topical corticosteroids seem not to work well on vesicular and weepy lesions. **Irritant contact dermatitis** is treated by protection from the irritant and use of topical corticosteroids as for atopic dermatitis (described above). The treatment of **allergic contact dermatitis** is detailed below.

B. Local Measures

1. Acute weeping dermatitis—Gentle cleansing and drying compresses (such as Domeboro) are recommended. Calamine lotion or zinc oxide paste may be used between wet dressings, especially for involvement of intertriginous areas or when oozing is not marked. Lesions on the extremities may be bandaged with wet dressings for 30–60 minutes several times a day. High-potency topical corticosteroids in gel or cream form (eg, fluocinonide, clobetasol, or halobetasol) may help suppress acute contact dermatitis and relieve itching. This treatment should be followed by tapering of the number of applications per day or use of a mid-potency corticosteroid, such as triamcinolone 0.1% cream, to prevent rebound of the dermatitis. A soothing formulation is 2 oz of 0.1% triamcinolone acetonide cream in 7.5 oz Sarna lotion (0.5% camphor, 0.5% menthol, 0.5% phenol) mixed by the patient.

2. Subacute dermatitis (subsiding)—Mid-potency (triamcinolone 0.1%) to high-potency corticosteroids (clobetasol, fluocinonide, desoximetasone) are the mainstays of therapy.

3. Chronic dermatitis (dry and lichenified)—High-potency to superpotency corticosteroids are used in ointment form. Occlusion may be helpful on the hands.

C. Systemic Therapy

For acute severe cases, prednisone may be given orally for 12–21 days. Prednisone, 60 mg for 4–7 days, 40 mg for 4–7 days, and 20 mg for 4–7 days, without a further taper is one useful regimen. The key is to use enough corticosteroid (and as early as possible) to achieve a clinical effect and to taper slowly over 2–3 weeks to avoid rebound.

Prognosis

Allergic contact dermatitis is self-limited if reexposure is prevented but often takes 2–3 weeks for full resolution. Removal of the causative agent is paramount to avoid recurrences.

Brar KK. A review of contact dermatitis. Ann Allergy Asthma Immunol. 2021;126:32. [PMID: 33091591]
Nassau S et al. Allergic contact dermatitis. Med Clin North Am. 2020;104:61. [PMID: 31757238]

POMPHOLYX

ESSENTIALS OF DIAGNOSIS

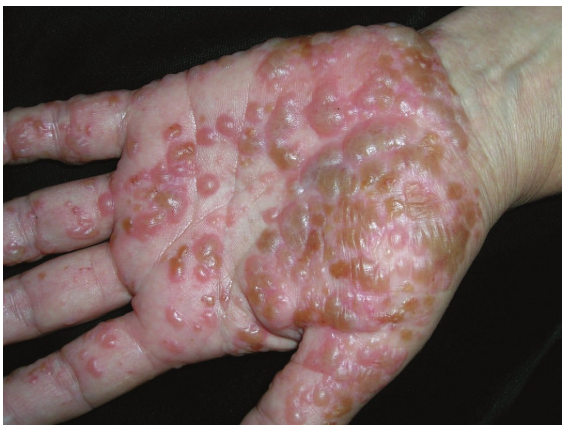
- Pruritic "tapioca" vesicles of 1–2 mm on the palms, soles, and sides of fingers.
- Vesicles may coalesce to form multiloculated blisters.
- Scaling and fissuring may follow drying of the blisters.
- Appearance in the third decade, with lifelong recurrences.

General Considerations

Pompholyx, or vesiculobullous dermatitis of the palms and soles, is formerly known as dyshidrosis or dyshidrotic eczema. About half of patients have an atopic background, and many patients report flares with stress. Patients with widespread dermatitis due to any cause may develop pompholyx-like eruptions as a part of an autoeczematization response.

Clinical Findings

Small clear vesicles resembling grains of tapioca stud the skin at the sides of the fingers and on the palms (Figure 6–28) and may also affect the soles, albeit less frequently. They may be associated with intense itching. Later, the vesicles dry and the area becomes scaly and fissured.



▲ **Figure 6–28.** Severe pompholyx. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Differential Diagnosis

Unroofing the vesicles and examining the blister roof with a KOH preparation will reveal hyphae in cases of bullous tinea. Patients with inflammatory tinea pedis may have a vesicular autoeczematization of the palms. NSAIDs may produce an eruption very similar to that of vesiculobullous dermatitis on the hands.

Prevention

There is no known way to prevent attacks if the condition is idiopathic. About one-third to one-half of patients with vesiculobullous hand dermatitis have a relevant contact allergen, especially nickel. Patch testing and avoidance of identified allergens can lead to improvement.

Treatment

Topical and systemic corticosteroids help some patients dramatically; however systemic corticosteroids are generally not appropriate therapy. A high-potency topical corticosteroid used early may help abort the flare and ameliorate pruritus. Topical corticosteroids are also important in treating the scaling and fissuring that are seen after the vesicular phase. Oral alitretinoin may be effective. It is essential that patients avoid anything that irritates the skin; they should wear cotton gloves inside vinyl gloves when doing dishes or other wet chores and use a hand cream after washing the hands. Patients respond to PUVA therapy and injection of botulinum toxin into the palms as for hyperhidrosis.

Prognosis

For most patients, the disease is an inconvenience. For some, vesiculobullous hand eczema can be incapacitating.

Agner T et al. Hand eczema: epidemiology, prognosis and prevention. J Eur Acad Dermatol Venereol. 2020;34:4. [PMID: 31860734]
Elsner P et al. Hand eczema: treatment. J Eur Acad Dermatol Venereol. 2020;34:13. [PMID: 31860736]

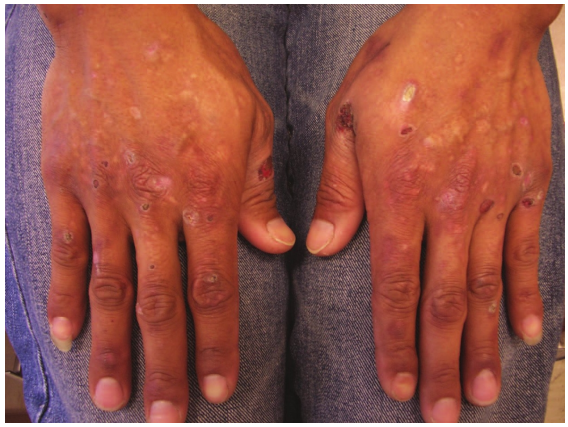
PORPHYRIA CUTANEA TARDA

ESSENTIALS OF DIAGNOSIS

- Noninflammatory blisters on sun-exposed sites, especially the dorsal surfaces of the hands.
- Hypertrichosis, skin fragility.
- Associated liver disease.
- Elevated urine porphyrins.

General Considerations

Porphyria cutanea tarda is the most common type of porphyria. Cases are sporadic or hereditary. The disease is associated with ingestion of certain medications (eg, estrogens) and alcoholic liver disease, hemochromatosis, or hepatitis C.



▲ **Figure 6–29.** Porphyria cutanea tarda of hands in patient with darker skin. (Used, with permission, from Kanade Shinkai, MD.)

Clinical Findings

A. Symptoms and Signs

Patients complain of painless blistering and fragility of the skin of the dorsal surfaces of the hands (Figure 6–29). Facial hypertrichosis and hyperpigmentation are common.

B. Laboratory Findings

Urinary uroporphyrins are elevated twofold to fivefold above coproporphyrins. Patients may also have abnormal liver biochemical tests, evidence of hepatitis C infection, increased liver iron stores, and hemochromatosis gene mutations.

Differential Diagnosis

Skin lesions identical to those of porphyria cutanea tarda may be seen in patients who undergo dialysis and in those who take certain medications (tetracyclines, voriconazole, and NSAIDs, especially naproxen). In this so-called pseudoporphyria, the biopsy results are the same as those associated with porphyria cutanea tarda, but urine porphyrins are normal.

Prevention

Barrier sun protection with clothing is required. Although the lesions are triggered by sun exposure, the wavelength of light triggering the lesions is beyond that absorbed by sunscreens.

Treatment

Stopping all triggering medications and substantially reducing or stopping alcohol consumption alone may lead to improvement in most cases. Phlebotomy at a rate of 1 unit every 2–4 weeks will gradually lead to improvement. Very low-dose antimalarial medication (as low as 200 mg of hydroxychloroquine orally twice weekly), alone or in combination with phlebotomy, increases porphyrin excretion and improves the skin disease. Deferasirox, an iron chelator, can also be beneficial. Treatment is continued until the patient is asymptomatic. Urine porphyrins may be monitored.

Prognosis

Most patients improve with treatment. Sclerodermoid skin lesions may develop on the trunk, scalp, and face.

Neeleman RA et al. Diagnostic and therapeutic strategies for porphyrias. Neth J Med. 2020;78:149. [PMID: 32641543]

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis is an uncommon disease manifested by intensely pruritic papules, vesicles, and papulovesicles mainly on the elbows, knees, buttocks, posterior neck, and scalp. It is associated with HLA antigens -B8, -DR3, and -DQ2. The histopathology is distinctive. Circulating antibodies to tissue transglutaminase are present in 90% of cases. NSAIDs may cause flares. Patients may have gluten-sensitive enteropathy. Three-fourths of patients have villous atrophy on small bowel biopsy; however, GI symptoms are subclinical in most. The prevalence of dermatitis herpetiformis to celiac disease is 1:8. Ingestion of gluten is the cause of dermatitis herpetiformis, and strict long-term avoidance of dietary gluten may eliminate the need for treatment or decrease the dose of dapsone (initial treatment dose is 100–200 mg orally daily) required to control the disease. Patients with dermatitis herpetiformis are at increased risk for GI lymphoma, and this risk is reduced by a gluten-free diet.

Reunala T et al. Dermatitis herpetiformis: an update on diagnosis and management. Am J Clin Dermatol. 2021;22:329. [PMID: 33432477]
Salmi T et al. Current concepts of dermatitis herpetiformis. Acta Derm Venereol. 2020;100:adv00056. [PMID: 32039457]

PEMPHIGUS

ESSENTIALS OF DIAGNOSIS

- Relapsing crops of bullae, often fragile and leading to erosions.
- Often preceded by mucous membrane bullae, erosions, and ulcerations.
- Superficial detachment of the skin after pressure or trauma variably present (Nikolsky sign).
- Acantholysis on biopsy.
- Immunofluorescence studies and serum ELISA for pathogenic antibodies are confirmatory.

General Considerations

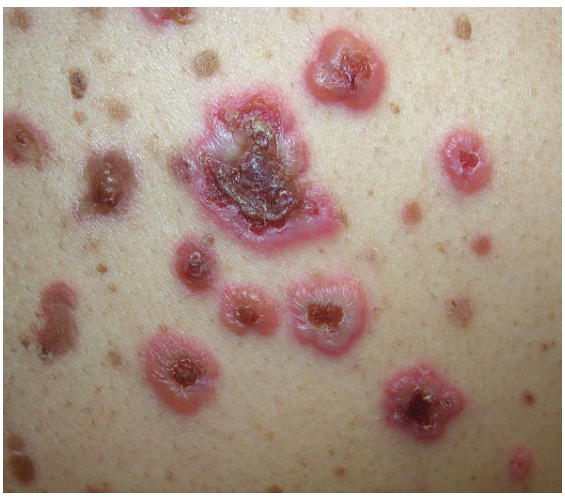
Pemphigus is an uncommon intraepidermal blistering disease occurring on skin and mucous membranes.

It is caused by autoantibodies to adhesion molecules expressed in the skin and mucous membranes. The bullae appear spontaneously and are tender and painful when they rupture. Drug-induced pemphigus has been reported. There are several forms of pemphigus: pemphigus vulgaris and its variant, pemphigus vegetans; and the more superficially blistering pemphigus foliaceus and its variant, pemphigus erythematosus. All forms may present at any age but most commonly in middle age. The vulgaris form begins in the mouth in over 50% of cases. The foliaceus form may be associated with other autoimmune diseases or may be drug-induced. Paraneoplastic pemphigus, a unique form of the disorder, is associated with numerous benign and malignant neoplasms, most frequently chronic lymphocytic leukemia, Castleman disease, B cell lymphoma, plasmacytoma, and thymoma. Associated bronchiolitis obliterans is characteristic.

Clinical Findings

A. Symptoms and Signs

Pemphigus is characterized by an insidious onset of flaccid bullae, crusts, and erosions in crops or waves (Figure 6–30). In pemphigus vulgaris, lesions often appear first on the oral mucous membranes. These rapidly become erosive. The scalp is another site of early involvement. Rubbing a cotton swab or finger laterally on the surface of uninvolved skin may cause easy separation of the epidermis (Nikolsky sign). Downward pressure on a fresh bulla may cause lateral spread (Asboe-Hansen sign). Pemphigus vegetans presents as erosive vegetating plaques, most often in intertriginous areas. Pemphigus foliaceus is a superficial form of pemphigus where cutaneous lesions present as flaccid bullae that quickly evolve into superficial erosions and thin pink plaques with overlying scale. Mucosal lesions are rare in pemphigus foliaceus. Pemphigus erythematosus has overlapping features of pemphigus foliaceus and lupus erythematosus. It presents with flaccid bullae that develop overlying scale and crust in a photodistributed area. Again, mucosal lesions are rare. Paraneoplastic pemphigus is histologically and immunologically distinct from other forms of the disease. Oral lesions predominate and cutaneous erythematous plaques resembling erythema multiforme are characteristic. Survival rates are low because of the underlying malignancy.



▲ **Figure 6–30.** Pemphigus vulgaris on the back with crusted and intact bullae. (Used, with permission, from Eric Kraus, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

B. Laboratory Findings

The diagnosis is made by light microscopy, direct and indirect immunofluorescence (IIF) microscopy, and ELISA assays to detect autoantibodies to intercellular adhesion molecules (desmoglien 3 and 1).

Differential Diagnosis

Blistering diseases include erythema multiforme, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), drug eruptions, bullous impetigo, contact dermatitis, dermatitis herpetiformis, and bullous pemphigoid, but flaccid blisters are not typical of these diseases, and acantholysis is not seen on biopsy. All these diseases have clinical characteristics and immunofluorescence test results that distinguish them from pemphigus. Pemphigus foliaceus must be distinguished from subacute cutaneous lupus erythematosus.

Complications

Secondary infection commonly occurs; this is a major cause of morbidity and mortality. Disturbances of fluid, electrolyte, and nutritional intake can occur as a result of painful oral ulcers.

Treatment

A. General Measures

Patients with severe disease should be hospitalized at bed rest and provided intravenous antibiotics and feedings as indicated. Anesthetic troches used before eating ease painful oral lesions.

B. Systemic Measures

Pemphigus requires systemic therapy as early in its course as possible. Initial therapy is with prednisone, 60–80 mg orally daily. In all but the mildest cases, a steroid-sparing agent is added from the beginning, since the disease course is long and the steroid-sparing agents take several weeks to exert their activity. Rituximab (1 g intravenously on days 1 and 15 as induction therapy followed by 500 mg intravenously every 6 months as maintenance therapy) is FDA approved for the treatment of pemphigus vulgaris, associated with induction of a complete remission, and considered by many experts to be first-line therapy. Repeated courses are efficacious and well tolerated in patients who do not achieve complete remission or relapse. Azathioprine (2–4 mg/kg orally daily) and mycophenolate mofetil (1–1.5 g orally twice daily) are other therapeutic options.

In refractory cases, monthly IVIG (2 g/kg intravenously over 3–4 days), pulse intravenous corticosteroids, cyclophosphamide, or plasmapheresis can be used.

C. Local Measures

In patients with limited disease, skin and mucous membrane lesions should be treated with topical corticosteroids. Complicating infection requires appropriate systemic and local antibiotic therapy.

Prognosis

Without antibiotic or corticosteroid treatment, the disease is fatal within 5 years. The course tends to be chronic in most patients; however, up to one-third experience remission. Infection is the most frequent cause of death, usually from *S aureus* septicemia.

Ellebrecht CT et al. Pemphigus and pemphigoid: from disease mechanisms to druggable pathways. J Invest Dermatol. 2022;142:907. [PMID: 34756581]
Lee MS et al. Network meta-analysis-based comparison of first-line steroid-sparing adjuvants in the treatment of pemphigus vulgaris and pemphigus foliaceus. J Am Acad Dermatol. 2021;85:176. [PMID: 32798583]
Werth VP et al; PEMPHIX Study Group. Rituximab versus mycophenolate mofetil in patients with pemphigus vulgaris. N Engl J Med. 2021;384:2295. [PMID: 34097368]

BULLOUS PEMPHIGOID

Bullous pemphigoid is a relatively benign pruritic disease characterized by tense blisters in flexural areas, usually remitting in 5 or 6 years, with a course characterized by exacerbations and remissions. Most affected persons are over the age of 60 and men are affected twice as frequently as women. The appearance of blisters may be preceded by pruritic urticarial or edematous lesions for months. Oral lesions are present in one-third. The disease may occur in various forms, including localized, vesicular, vegetating, erythematous, erythrodermic, and nodular. Drugs may induce bullous pemphigoid. The most common offender is furosemide. Immunotherapy for malignancies with PD-1 inhibitors can cause drug-induced bullous pemphigoid.

The diagnosis is made by biopsy with direct immunofluorescence examination and serum antibody testing. Light microscopy shows a subepidermal blister. With direct immunofluorescence, IgG and C3 are found at the dermal-epidermal junction. ELISA tests for bullous pemphigoid antibodies (BP 180 or BP 230) are 87% sensitive and 95% specific. If the patient has mild disease, ultrapotent topical corticosteroids may be adequate. Prednisone (0.75 mg/kg orally daily) is often used to achieve rapid control of more widespread disease. Tetracycline (500 mg orally three times daily) or doxycycline (100 mg orally twice a day), alone or combined with nicotinamide—not nicotinic acid or niacin—(up to 1.5 g orally daily), may control the disease in patients who cannot use corticosteroids or may allow for decreasing or eliminating corticosteroids after control is achieved. Dapsone (50–200 mg orally daily) is particularly effective in mucous membrane pemphigoid. If these medications are not effective, methotrexate (5–25 mg orally weekly), azathioprine (2–4 mg/kg orally daily), or mycophenolate mofetil (1–1.5 g orally twice daily) may be used as steroid-sparing agents. Intravenous immunoglobulin, rituximab, omalizumab, and dupilumab have been used with success in refractory cases.

Montagnon CM et al. Subepithelial autoimmune blistering dermatoses: Clinical features and diagnosis. J Am Acad Dermatol. 2021;85:1. [PMID: 33684496]
Tedbirt B et al. Mixed individual-aggregate data on all-cause mortality in bullous pemphigoid: a meta-analysis. JAMA Dermatol. 2021;157:421. [PMID: 33729430]

PUSTULAR DISORDERS

ACNE VULGARIS

ESSENTIALS OF DIAGNOSIS

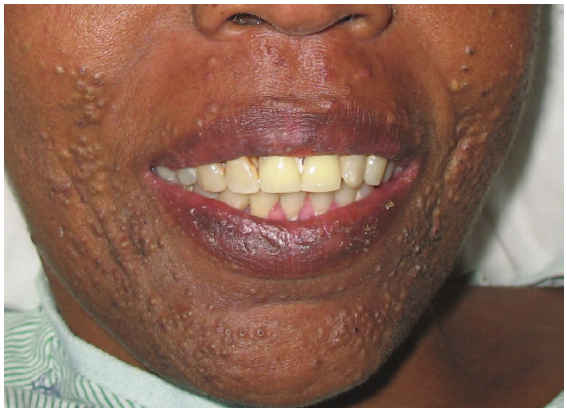
- Almost universal in puberty; may begin in premenarchal girls and present or persist into the fourth or fifth decade.
- Comedones are the hallmark. Severity varies from comedonal to papular or pustular inflammatory acne to cysts or nodules.
- Face, neck, and upper trunk may be affected.
- Scarring may be a sequela of the disease or picking by the patient.

General Considerations

Acne vulgaris is polymorphic. Open and closed comedones, papules, pustules, and cysts are found.

In younger persons, acne vulgaris is more common and more severe in males. Acne may persist into adulthood. Twelve percent of women and 3% of men over age 25 have acne vulgaris. This rate does not decrease until the fourth or fifth decade of life. The skin lesions parallel sebaceous activity. Pathogenic events include plugging of the infundibulum of the follicles, retention of sebum, overgrowth of the acne bacillus (*Cutibacterium acnes*) with resultant release of and irritation by accumulated fatty acids, and foreign-body reaction to extrafollicular sebum. Antibiotics may help control acne because of their antibacterial or anti-inflammatory properties.

Hyperandrogenism may be a cause of acne in women and may be accompanied by hirsutism or irregular menses. Polycystic ovary syndrome (PCOS) is the most common identifiable cause. Acne may develop in patients who use systemic corticosteroids or topical fluorinated corticosteroids on the face. Acne may be exacerbated or caused by cosmetic creams or oils as well as androgenic supplements or masculinizing hormone therapy in transgender individuals.



▲ **Figure 6–31.** Acne vulgaris. Extensive comedones and hyperpigmented macules are present in patient with dark skin. (Used, with permission, from Kanade Shinkai, MD.)

Clinical Findings

There may be mild tenderness, pain, or itching. The lesions occur mainly over the face, neck, upper chest, back, and shoulders. Comedones (tiny, flesh-colored, white or black noninflamed superficial papules that give the skin a rough texture or appearance) are the hallmark of acne vulgaris. Inflammatory papules, pustules, ectatic pores, acne cysts, and scarring are also seen (Figure 6–31).

Acne may have different presentations at different ages. Preteens often present with comedones as their first lesions. Inflammatory lesions in young teenagers are often found in the middle of the face, extending outward as the patient becomes older. Adult females may present with comedonal or papular lesions especially on the chin and jawline.

Differential Diagnosis

In adults, rosacea presents with papules and pustules in the middle third of the face, but absence of truncal involvement, telangiectasia, flushing, and the absence of comedones distinguish rosacea from acne vulgaris. A pustular eruption on the face in patients receiving antibiotics or with otitis externa should be investigated with culture to rule out a gram-negative folliculitis. Pustules on the face can also be caused by dermatophytic or demodex infection. Lesions on the back are more problematic. When they occur alone, staphylococcal folliculitis, miliaria ("heat rash") or, uncommonly, *Pityrosporum* folliculitis should be suspected. Bacterial culture, trial of an antistaphylococcal antibiotic, and observing the response to therapy will help in the differential diagnosis. In patients with HIV infection, folliculitis is common and may be either staphylococcal folliculitis or eosinophilic folliculitis (typically pruritic tumid papules on the face and neck).

Complications

Cyst formation, pigmentary changes, scarring, and poor quality of life may result.

Treatment

A. General Measures

1. Education of the patient—Education on proper use of medications and cosmetics is paramount. Because lesions take 4–6 weeks to improve, clinical improvement should be measured by the number of new lesions forming after 6–8 weeks of therapy. Additional time (3–4 months) will be required to see improvement on the back and chest, as these areas are slowest to respond. Avoid topical exposure to oils, cocoa butter (theobroma oil), and greases in cosmetics, including hair products. Scarring may occur with or without the patient manipulating the lesions. It is essential that the patient be educated in a supportive way about this complication. Anxiety and depression are common in patients with excoriated acne.

2. Diet—A low glycemic diet has been associated with improvement and lower incidence of acne. This improvement was associated with a reduction in insulin resistance. Hyperinsulinemia has also been associated with acne in both eumenorrheic women and individuals with PCOS.

B. Comedonal Acne

Treatment of acne is based on the type and severity of lesions. Comedones require treatment different from that of pustules and cystic lesions. In assessing severity, take the sequelae of the lesions into account. An individual who gets only a few new lesions per month that scar or leave postinflammatory hyperpigmentation must be treated much more aggressively than a comparable patient whose lesions clear without sequelae. Hygiene plays little role in acne treatment, and a mild soap is almost always recommended. The agents effective in comedonal acne are listed below in the order in which they should be tried.

1. Topical retinoids—Tretinoin is very effective for comedonal and papular acne, but its usefulness is limited by irritation. Start with 0.025% cream (not gel) and have the patient use it at first twice weekly at night, increasing frequency to nightly as tolerated. A few patients cannot tolerate this low-strength preparation more than three times weekly, which may still promote improvement. A lentil-sized amount is sufficient to cover the entire face. To avoid irritation, have the patient wait 20 minutes after washing to apply. For patients irritated by standard tretinoin preparations, other options are adapalene gel 0.1% and reformulated tretinoin (Renova, Retin A Micro, Avita). Although the absorption of tretinoin is minimal, its use during pregnancy is contraindicated. Patients should be warned that their acne may flare in the first 4 weeks of treatment.

2. Benzoyl peroxide—Benzoyl peroxide products are available in concentrations of 2.5%, 4%, 5%, 8%, and 10%, but 2.5% is as effective as 10% and less irritating. In general, water-based and not alcohol-based gels should be used to decrease irritation. Single formulations of benzoyl peroxide in combination with several other topical agents, including adapalene and topical antibiotics (erythromycin, clindamycin phosphate), are available.

C. Papular or Cystic Inflammatory Acne

Brief treatment (3 weeks to 3 months) with topical or oral antibiotics is the mainstay for treatment of inflammatory acne that does not respond to topical therapy with retinoids or benzoyl peroxide. Topical clindamycin phosphate and erythromycin are used only for mild papular acne or for patients who refuse or cannot tolerate oral antibiotics. To decrease resistance, benzoyl peroxide should be used in combination with the topical antibiotic.

1. Mild acne—The first choice of topical antibiotics in terms of efficacy and relative lack of induction of resistant *C acnes* is the combination of erythromycin or clindamycin with benzoyl peroxide topical gel or wash (Table 6–2). These may be used once or twice daily. The addition of tretinoin cream or gel at night may increase improvement since it works via a different mechanism. Topical retinoids should be used for long-term maintenance therapy.

2. Moderate acne—Common oral antibiotics used for acne include doxycycline (100 mg twice daily), minocycline (50–100 mg once or twice daily), TMP-SMZ (one double-strength tablet twice daily), or a cephalosporin (cefadroxil or cephalexin 500 mg twice daily), which should be used in combination with benzoyl peroxide to minimize development of antibiotic resistance. It may take 3 months or more for truncal acne to resolve with oral antibiotic treatment. In general, discontinuing antibiotics immediately without adjunctive topical therapy results in prompt recurrence. Topical retinoids are excellent for long-term maintenance following antibiotics. Subantimicrobial dosing of doxycycline (40–50 mg orally daily) can be used in patients who require long-term systemic therapy. Combination oral contraceptives or spironolactone (50–200 mg orally daily) are highly effective alternatives in women with treatment-resistant acne. Tetracycline, minocycline, and doxycycline are contraindicated in pregnancy, but certain oral erythromycins or cephalosporins may be used.

3. Severe acne—

A. Isotretinoin—A vitamin A analog, isotretinoin is used for the treatment of severe acne that has not responded to conventional therapy. An oral dosage of 0.5–1 mg/kg/day for 20 weeks for a cumulative dose of at least 120 mg/kg is usually adequate for treating and preventing the recurrence of severe cystic acne. Patients should be offered isotretinoin therapy before they experience significant acne scarring. *Isotretinoin is absolutely contraindicated during pregnancy because of its teratogenicity.* Two forms of effective contraception must be used; abstinence is an acceptable alternative. Informed consent must be obtained before its use, and patients must be enrolled in a monitoring program (iPledge). In addition to its teratogenicity, isotretinoin has numerous side effects and should only be prescribed by clinicians well aware of these issues. Cheilitis, dry skin, and photosensitivity are almost universal side effects. Consider ordering laboratory tests, including total cholesterol levels, triglyceride levels, and liver enzyme tests (particularly ALT, which is the most liver-specific enzyme), in patients before treatment and after achieving therapeutic dosing; monitoring through the entire treatment may not be high value. Monthly pregnancy testing is required for premenopausal women.

Abnormal laboratory tests, especially elevated liver enzymes and triglyceride levels, return to normal quickly upon conclusion of therapy. The medication may induce long-term remissions in 40–60%, or acne may recur that is more easily controlled with conventional therapy. Occasionally, a second course is needed if acne does not respond or recurs.

B. Intralesional injection—Intralesional injection of dilute suspensions of triamcinolone acetonide (2.5 mg/mL, 0.05 mL per lesion) will often hasten the resolution of deeper papules and occasional cysts.

C. Scar revision—Cosmetic improvement may be achieved by excision and punch-grafting of deep scars and by physical or chemical abrasion of inactive acne lesions, particularly flat, superficial scars.

Prognosis

Acne vulgaris eventually remits spontaneously, but when this will occur cannot be predicted. The condition may persist throughout adulthood and may lead to severe scarring if left untreated. Patients treated with antibiotics continue to improve for the first 3–6 months of therapy. Relapse during treatment may suggest the emergence of resistant *C acnes*. The disease is chronic and tends to flare intermittently despite treatment. Remissions following systemic treatment with isotretinoin may be lasting in up to 60% of cases. Relapses after isotretinoin usually occur within 3 years and require a second course in up to 20% of patients.

Kurokawa I et al. Recent advances in understanding and managing acne. F1000Res. 2020;9:792. [PMID: 32765835]
Sadeghzadeh-Bazargan A et al. Systematic review of low-dose isotretinoin for treatment of acne vulgaris: focus on indication, dosage, regimen, efficacy, safety, satisfaction, and follow up, based on clinical studies. Dermatol Ther. 2021;34:e14438. [PMID: 33085149]

ROSACEA

ESSENTIALS OF DIAGNOSIS

- A chronic disorder affecting the face.
- Neurovascular component: erythema and telangiectasis and a tendency to flush easily.
- Acneiform component: papules and pustules may be present.
- Glandular component: sebaceous hyperplasia and fibrosis of affected areas (eg, rhinophyma).

General Considerations

Rosacea is a common condition that presents in adulthood. The pathogenesis of this chronic disorder is not known.

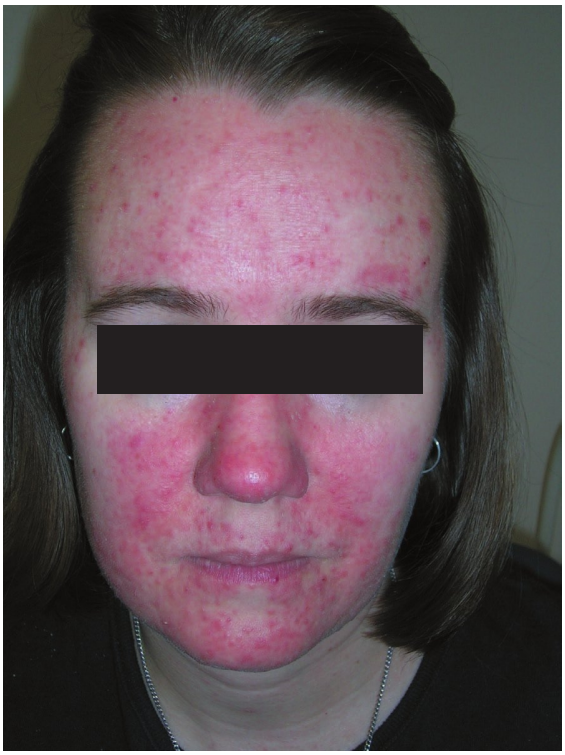
Topical corticosteroids applied to the face can induce rosacea-like conditions.

Clinical Findings

Patients frequently report flushing or exacerbation of their rosacea due to heat, hot drinks, spicy food, sunlight, exercise, alcohol, emotions, or menopausal flushing. The cheeks, nose, chin, and ears—at times the entire face—may be affected. No comedones are seen. In its mildest form, erythema and telangiectasias are seen on the cheeks. Inflammatory papules may be superimposed on this background and may evolve to pustules (Figure 6–32). Associated seborrhea may be found. Some patients complain of burning or stinging with episodes of flushing and extremely cosmetic-intolerant skin. Patients may have associated ophthalmic disease, including blepharitis, keratitis, and chalazion, which often requires topical or systemic antibiotic or immunosuppressive therapy.

Differential Diagnosis

Rosacea is distinguished from acne by the presence of the neurovascular component and the absence of comedones. Lupus is often misdiagnosed, but the presence of pustules excludes that diagnosis.



▲ **Figure 6–32.** Rosacea in a 34-year-old woman showing erythema, papules, and pustules covering much of the face. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Treatment

Educating patients to avoid the factors they know to produce exacerbations is important. Patients should wear a broad-spectrum mineral-based sunscreen; zinc- or titanium-based sunscreens are tolerated best. Medical management is most effective for the inflammatory papules and pustules and the erythema that surrounds them. Rosacea is usually a lifelong condition, so maintenance therapy is required. Most treatments target the papulopustular and cystic components. Only certain topical agents (brimonidine and oxymetazoline) and laser benefit erythema. Telangiectasias are benefited by laser therapy, and phymatous overgrowth of the nose can be treated by surgical reduction. Rhinophyma must be managed using surgical reduction.

A. Local Therapy

Avoidance of triggers (especially alcohol and spicy or hot foods) and drinking ice water may be effective in reducing facial erythema and flushing. Metronidazole (cream, gel, or lotion), 0.75% applied twice daily or 1% applied once daily, and ivermectin 1% cream applied once daily are effective topical treatments. Another effective treatment includes topical clindamycin (solution, gel, or lotion) 1% applied twice daily. Response is noted in 4–8 weeks. Sulfur-sodium sulfacetamide-containing topicals are helpful in patients only partially responsive to topical antibiotics. Topical retinoids or topical tacrolimus ointment (0.1%) can be carefully added for maintenance. Topical brimonidine tartrate gel 0.33% or oxymetazoline 1% cream can temporarily reduce the erythema, and laser treatment has longer-term benefit for erythema.

B. Systemic Therapy

Oral tetracyclines should be used when topical therapy is inadequate. Minocycline or doxycycline, 50–100 mg orally once or twice daily, is effective. Metronidazole or amoxicillin, 250–500 mg orally twice daily, or rifaximin, 400 mg orally three times daily (for 10 days), may be used in refractory cases. Side effects are few, although metronidazole may cause a disulfiram-like effect when the patient ingests alcohol and neuropathy with long-term use. Long-term maintenance with subantimicrobial dosing of minocycline or doxycycline is recommended once the initial flare of rosacea has resolved. Isotretinoin may succeed where other measures fail. A dosage of 0.5 mg/kg/day orally for 12–28 weeks is recommended, although very low-dose isotretinoin may also be effective. See precautions above.

Prognosis

Rosacea tends to be a persistent process. With the regimens described above, it can usually be controlled adequately.

Alexis AF et al. Global epidemiology and clinical spectrum of rosacea, highlighting skin of color: review and clinical practice experience. J Am Acad Dermatol. 2019;80:1722. [PMID: 30240779]

Tan J et al. Treating inflammation in rosacea: current options and unmet needs. J Drugs Dermatol. 2020;19:585. [PMID: 32574018]

MILIARIA (Heat Rash)

ESSENTIALS OF DIAGNOSIS

- Burning, itching, superficial aggregated small vesicles, papules, or pustules on covered areas of the skin, usually the trunk.
- More common in hot, moist climates.
- Rare forms associated with fever and even heat prostration.

General Considerations

Miliaria occurs most commonly on the trunk and intertriginous areas. A hot, moist environment is the most frequent cause. Occlusive clothing, fever while bedridden, and medications that enhance sweat gland function (eg, clonidine, beta-blockers, opioids) may increase the risk. Plugging of the ostia of sweat ducts occurs, with ultimate rupture of the sweat duct, producing an irritating, stinging reaction.

Clinical Findings

The usual symptoms are burning and itching. The histologic depth of sweat gland obstruction determines the clinical presentation: miliaria crystallina in the superficial (subcorneal) epidermis, miliaria rubra in the deep epidermis, and miliaria profunda in the dermis. The lesions consist of small (1–3 mm) nonfollicular lesions. Subcorneal thin-walled, discrete clear fluid-filled vesicles are termed "miliaria crystallina." When fluid is turbid and lesions present as vesicopustules or pustules, they are called miliaria pustulosa. Miliaria rubra (prickly heat) presents as pink papules. Miliaria profunda presents as nonfollicular skin-colored papules that develop after multiple bouts of miliaria rubra. In a hospitalized patient, the reaction virtually always affects the back.

Differential Diagnosis

Miliaria is to be distinguished from a drug eruption and folliculitis.

Prevention

Use of a topical antibacterial preparation, such as chlorhexidine, prior to exposure to heat and humidity may help prevent the condition. Frequent turning or sitting of the hospitalized patient may reduce miliaria on the back.

Treatment

The patient should keep cool and wear light clothing. A mid-potency corticosteroid (triamcinolone acetonide, 0.1%) in a lotion or cream may be applied two to four times daily. Secondary infections (superficial pyoderma) are treated with appropriate antistaphylococcal antibiotics. Anticholinergic medications (eg, glycopyrrolate 1 mg orally twice a day or topically applied) may be helpful in severe cases.

Prognosis

Miliaria is usually a mild disorder, but severe forms (tropical anhidrosis and asthenia) result from interference with the heat-regulating mechanism.

Rouai M et al. Miliaria crystallina in an intensive care patient. Clin Case Rep. 2021;9:e04665. [PMID: 34430023]

ERYTHEMAS

REACTIVE ERYTHEMAS

URTICARIA & ANGIOEDEMA

ESSENTIALS OF DIAGNOSIS

- Evanescent wheals or hives with or without angioedema.
- Intense itching; very rarely, pruritus may be absent.
- Urticaria is divided into acute and chronic forms.
- Most episodes are acute and self-limited (1–2 weeks).
- Chronic urticaria (lasting > 6 weeks) may have an autoimmune basis.

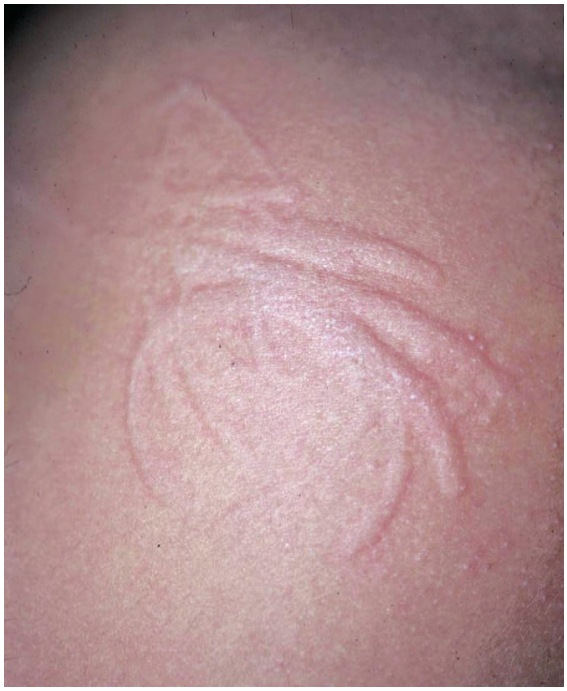
General Considerations

Urticaria involves hives, angioedema or both. It may be acute or chronic (more than 6 weeks' duration). Chronic urticaria is further divided into chronic spontaneous urticaria and chronic inducible urticaria. Chronic inducible urticaria is reproducibly triggered by specific exposures. Examples include cholinergic urticaria, solar urticaria, cold urticaria, dermatographism, and delayed pressure urticaria. True urticaria should be differentiated from diseases that present with similar lesions that are not true urticaria (eg, adult-onset Still disease, urticarial vasculitis, and cryopyrin-associated periodic syndromes). Some patients with chronic spontaneous urticaria demonstrate autoantibodies directed against mast cell IgE receptors.

Clinical Findings

A. Symptoms and Signs

Lesions are itchy, red swellings of a few millimeters to many centimeters (Figure 6–33). The morphology of the lesions may vary over a period of minutes to hours, resulting in geographic or bizarre patterns. Individual lesions in true urticaria last less than 24 hours and often only 2–4 hours. Angioedema is involvement of deeper subcutaneous tissue with swelling of the lips, eyelids, palms, soles, and genitalia.



▲ **Figure 6–33.** Urticaria. (Used, with permission, from TG Berger, MD, Dept Dermatology, UCSF.)

Angioedema is no more likely than urticaria to be associated with systemic complications, such as laryngeal edema or hypotension. Dermatographism is induced by scratching and can be elicited during the clinic visit by scratching the patient's skin. The wheals of cholinergic urticaria are 2–3 mm in diameter with a large surrounding red flare.

B. Laboratory Findings

The most common causes of acute urticaria are foods, upper respiratory infections, and medications. The cause of chronic spontaneous urticaria is often not found. Although laboratory studies are not generally helpful in the evaluation of acute or chronic urticaria, a CBC with differential, ESR, CRP, TSH, and liver biochemical tests may be appropriate for some patients with chronic urticaria. Elevated inflammatory markers suggest an alternate diagnosis. In patients with individual lesions that persist past 24 hours, skin biopsy may confirm neutrophilic urticaria or urticarial vasculitis. A functional ELISA test looking for antibodies against the high-affinity receptor for IgE (Fc-Epislon RI) can detect patients with an autoimmune basis for their chronic urticaria.

Differential Diagnosis

Papular urticaria resulting from insect bites persists for days. A central punctum can usually be seen. Streaked urticarial lesions may be seen in the 24–48 hours before blisters appear in acute allergic plant dermatitis, eg, poison ivy, oak, or sumac. Urticarial responses to heat, sun, water, and pressure are quite rare. Urticarial vasculitis is defined as cutaneous vasculitis where the skin lesions clinically mimic urticaria. Lesions last longer than 24 hours and often sting or burn rather than itch. Patients do not respond to antihistamines. Urticarial vasculitis may be caused by viral hepatitis and may be seen as part of serum sickness. In hereditary angioedema, there is generally a positive family history and GI or respiratory symptoms. Wheals are not part of the syndrome, and lesions are not pruritic.

Treatment

A. General Measures

The etiology of acute urticaria is found in less than half of cases. The etiology of chronic urticaria is found in even fewer cases. In general, a careful history and physical examination are helpful but extensive costly workups for chronic spontaneous urticaria are not indicated. Patients with chronic autoimmune urticaria may have other autoimmune diseases and be more difficult to treat. In cases of chronic inducible urticaria, exposure to physical factors, such as heat, cold, sunlight, pressure, heat induced by exercise, excitement, and hot showers, should be modulated.

B. Systemic Treatment

The mainstay of treatment initially includes H_1-antihistamines, often starting with second-generation antihistamines. Second-generation H_1-antihistamines include fexofenadine (180 mg orally once daily) or cetirizine or loratadine (10 mg orally daily). Less than 40% of chronic urticaria cases respond to standard H_1-blockade, and higher doses of second-generation antihistamines (up to four times the standard recommended dose) increase the likelihood of response to therapy to 60%. Combining antihistamines (eg, fexofenadine plus cetirizine) at these higher doses can be done safely to achieve remission in refractory cases. First-generation H_1-antihistamines such as hydroxyzine, 10–25 mg orally two or three times daily, or as a single nightly dose of 25–75 may be added to this regimen.

Cyproheptadine, 4 mg orally four times daily, may be especially useful for cold urticaria.

Doxepin (a tricyclic antidepressant with potent antihistaminic properties), 10–75 mg orally at bedtime, can be very effective in chronic urticaria. It has anticholinergic side effects.

If a skin biopsy of a lesion of chronic urticaria identifies neutrophils as a significant component of the inflammatory infiltrate, dapsone or colchicine (or both) may be useful.

Although systemic corticosteroids in a dose of about 40 mg daily will usually suppress acute and chronic urticaria, corticosteroids are rarely indicated and, once withdrawn, urticaria virtually always returns. Therefore, consultation with a dermatologist or an allergist who has experience in managing severe urticaria is recommended before initiating systemic corticosteroid therapy. Omalizumab is approved for the treatment of refractory chronic urticaria and should be considered when severe chronic urticaria fails to respond to high-dose antihistamines.

C. Local Treatment

Local treatment is rarely rewarding.

Prognosis

Acute urticaria usually lasts only a few days to weeks. Half of patients whose urticaria persists for longer than 6 weeks will have it for years.

Agache I et al. Efficacy and safety of treatment with omalizumab for chronic spontaneous urticaria: a systematic review for the EAACI Biologicals Guidelines. Allergy. 2021;76:59. [PMID: 32767573]
Gonçalo M et al. The global burden of chronic urticaria for the patient and society. Br J Dermatol. 2021;184:226. [PMID: 32956489]
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ERYTHEMA MULTIFORME/ STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

ESSENTIALS OF DIAGNOSIS

Erythema multiforme

- Herpes simplex is most common cause.
- Cutaneous lesions are true three ring targets.
- Presents on the extensor surfaces, palms, soles, or mucous membranes.
- Disease remains localized.

Stevens-Johnson syndrome and toxic epidermal necrolysis

- Stevens-Johnson syndrome: < 10% BSA detachment.
- Stevens-Johnson syndrome/toxic epidermal necrolysis overlap: 10–30% BSA detachment.
- Toxic epidermal necrolysis: > 30% BSA detachment.
- Medications are most common cause.
- Cutaneous lesions are targetoid but often not true three ring targets.
- Favors the trunk.
- Involves two or more mucous membranes.
- May progress to significant BSA involvement and may be life-threatening.

General Considerations

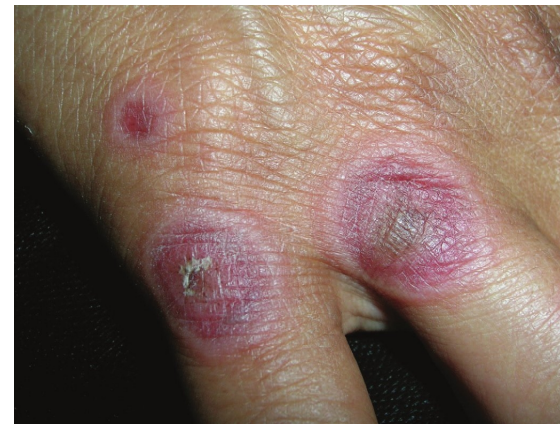
Erythema multiforme is an acute inflammatory skin disease that was traditionally divided into minor and major types based on the clinical findings. Approximately 90% of cases of erythema multiforme minor follow outbreaks of herpes simplex and is preferably termed "herpes-associated erythema multiforme." The term "erythema multiforme major" has largely been abandoned.

SJS is defined as atypical target lesions with less than 10% BSA detachment; TEN is defined as lesions with greater than 30% BSA detachment; and patients with SJS/TEN overlap have between 10% and 30% BSA detachment. The abbreviation SJS/TEN is often used to refer to these three variants of what is considered one syndrome. SJS/TEN is characterized by toxicity and involvement of two or more mucosal surfaces (often oral and conjunctival but can involve any mucosal surface, including respiratory epithelium). SJS/TEN is most often caused by oral or, less commonly, topical medications, especially sulfonamides, NSAIDs, allopurinol, and anticonvulsants. In certain races, polymorphisms of antigen-presenting major histocompatibility (MHC) loci increase the risk for the development of SJS/TEN. *Mycoplasma pneumoniae* may trigger a mucocutaneous reaction with skin and oral lesions closely resembling SJS in children/young adults, which tends not to progress to TEN-like disease and carries an overall good prognosis.

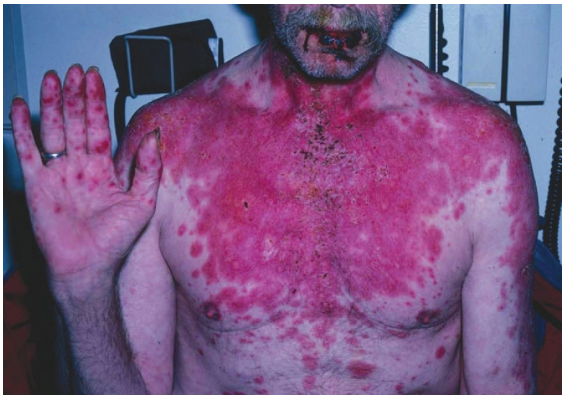
Clinical Findings

A. Symptoms and Signs

A classic target lesion, as in herpes-associated erythema multiforme, consists of three concentric zones of color change, most often on acral surfaces (hands, feet, elbows, and knees) (Figure 6–34). SJS/TEN presents with raised purpuric target-like lesions, with only two zones of color change and a central blister, or nondescript reddish or purpuric macules favoring the trunk and proximal upper extremities (Figure 6–35). Pain on eating, swallowing, and urination can occur if relevant mucosae are involved.



▲ **Figure 6–34.** Erythema multiforme with classic target lesions. Note the three zones of color change. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)



▲ **Figure 6–35.** Stevens-Johnson syndrome. (Used, with permission, from TG Berger, MD, Dept Dermatology, UCSF.)

B. Laboratory Findings

Skin biopsy is diagnostic. Direct immunofluorescence studies are negative. Blood tests are not useful for diagnosis.

Differential Diagnosis

Urticaria and drug eruptions are the chief entities that must be differentiated from erythema multiforme. In true urticaria, lesions are not purpuric or bullous, last less than 24 hours, and respond to antihistamines. Urticaria multiforme is a distinct eruption in infants and young children and presents with fever and targetoid urticarial plaques. The differential diagnosis of SJS/TEN includes autoimmune bullous diseases (eg, pemphigus vulgaris, bullous pemphigoid, and linear IgA bullous dermatosis), acute SLE, vasculitis, and Sweet syndrome. The presence of a blistering eruption requires biopsy and dermatologic consultation for appropriate diagnosis and treatment.

Complications

The tracheobronchial mucosa, conjunctiva, genital, and urethral mucosa may be involved and may result in scarring in severe cases. *Ophthalmologic consultation is required if ocular involvement is present because vision loss is the major consequence of SJS/TEN.*

Treatment

A. General Measures

Toxic epidermal necrolysis is best treated in an acute care environment, which may include an ICU or a burn unit. Patients should be admitted if mucosal involvement interferes with hydration and nutrition or extensive blistering develops. Open lesions should be managed like second-degree burns. Immediate discontinuation of the inciting medication (before blistering occurs) is a significant predictor of outcome. Delay in establishing the diagnosis and inadvertently continuing the offending medication results in higher morbidity and mortality.

B. Specific Measures

Oral and topical corticosteroids are useful in the oral variant of erythema multiforme. Oral acyclovir prophylaxis of herpes simplex infections may be effective in preventing recurrent herpes-associated erythema multiforme minor.

The most important aspect of treatment for SJS/TEN is to stop the offending medication and to move patients with greater than 25–30% BSA involvement to an appropriate acute care environment. Nutritional and fluid support and high vigilance for infection are the most important aspects of care. Reviews of systemic treatments for SJS and TEN have been conflicting. Some data support the use of high-dose corticosteroids. If corticosteroids are tried, they should be used early, before blistering occurs, and in high doses (prednisone, 1–2 mg/kg/day). Intravenous immunoglobulin (IVIG) (1 g/kg/day for 4 days) used early in the course has resulted in decreased mortality in some studies. Cyclosporine (3–5 mg/kg/day for 7 days) may also be effective. Etanercept is the treatment of choice in some centers.

C. Local Measures

Topical corticosteroids are not very effective in this disease (except the oral variant).

Prognosis

Erythema multiforme minor usually lasts 2–6 weeks and may recur. SJS/TEN may be serious with a mortality of 30% in cases with greater than 30% BSA involvement. The ABCD-10 and SCORTEN are severity of illness scales that predict mortality in SJS/TEN.

Grünwald P et al. Erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis—diagnosis and treatment. J Dtsch Dermatol Ges. 2020;18:547. [PMID: 32469468]

Torres-Navarro I et al. Systemic therapies for Stevens-Johnson syndrome and toxic epidermal necrolysis: a SCORTEN-based systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2021;35:159. [PMID: 32946187]

Zhang S et al. Biologic TNF-alpha inhibitors in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis: a systemic review. J Dermatolog Treat. 2020;31:66. [PMID: 30702955]

EXFOLIATIVE DERMATITIS (Exfoliative Erythroderma)

ESSENTIALS OF DIAGNOSIS

- Desquamation and erythema over most of the body.
- Itching, malaise, fever, chills, weight loss.

General Considerations

Erythroderma describes generalized redness and desquamation of more than 30% of the skin surface. A preexisting dermatosis is the cause of exfoliative dermatitis in

two-thirds of cases, including psoriasis, atopic dermatitis, contact dermatitis, pityriasis rubra pilaris, and seborrheic dermatitis. Reactions to topical or systemic medications account for about 15% of cases, cancer (paraneoplastic symptom of lymphoma, solid tumors, and most commonly, cutaneous T-cell lymphoma) for 10%, and 10% are idiopathic. Widespread scabies is an important consideration since patients with erythrodermic presentation are highly contagious. At the time of acute presentation, without a clear-cut prior history of skin disease or medication exposure, it may be impossible to make a specific diagnosis of the underlying condition, and diagnosis may require continued observation.

Clinical Findings

A. Symptoms and Signs

Symptoms may include itching, weakness, malaise, fever, and weight loss. Chills are prominent. Erythema and desquamation are widespread. Loss of hair and nails can occur. Generalized lymphadenopathy may be due to lymphoma or leukemia or may be reactive. The mucosae are typically spared.

B. Laboratory Findings

A skin biopsy is required and may show changes of a specific inflammatory dermatitis or cutaneous T-cell lymphoma. Peripheral leukocytes may show clonal rearrangements of the T-cell receptor in Sézary syndrome.

Complications

Protein and electrolyte loss as well as dehydration may develop in patients with generalized inflammatory exfoliative erythroderma; sepsis may occur.

Treatment

A. Topical Therapy

Home treatment is with cool to tepid baths and application of mid-potency corticosteroids under wet dressings or with occlusion with plastic wrap. If the condition becomes unmanageable in an outpatient setting, the patient should be hospitalized.

B. Specific Measures

Stop all medications, if possible. Systemic corticosteroids may provide marked improvement in severe or fulminant exfoliative dermatitis but should be avoided long-term (see Chapter 26). For cases of psoriatic erythroderma and pityriasis rubra pilaris, acitretin, methotrexate, cyclosporine, or a TNF inhibitor may be indicated. Erythroderma secondary to lymphoma or leukemia requires specific topical or systemic chemotherapy. Suitable antibiotic medications with coverage for *Staphylococcus* should be given when there is evidence of bacterial infection.

Prognosis

Careful follow-up is necessary because identifying the cause of exfoliative erythroderma early in the course of the disease may be impossible. Most patients improve or recover completely but some require long-term therapy. Deaths are rare in the absence of cutaneous T-cell lymphoma. A minority of patients will suffer from undiminished erythroderma for indefinite periods.

Reynolds KA et al. A systematic review of treatment strategies for erythrodermic psoriasis. J Dermatolog Treat. 2021;32:49. [PMID: 31682547]

PHOTODERMATITIS

ESSENTIALS OF DIAGNOSIS

- Painful or pruritic erythema, edema, or vesiculation on sun-exposed surfaces (face, neck, hands, and "V" of the chest).
- Inner upper eyelids and area under the chin are spared.

General Considerations

Photodermatitis is a cutaneous reaction to UV radiation. It comprises four groups: (1) primary, idiopathic immunologically mediated photodermatoses; (2) drug- or chemical-induced photodermatoses; (3) dermatoses that are worsened or aggravated by UV exposure; and (4) genetic diseases with mutations predisposing to photodermatitis.

Primary photodermatoses include polymorphic light eruption, chronic actinic dermatitis, and actinic prurigo. Drug- or chemical-induced photodermatitis may be either exogenous or endogenous in origin. Porphyria cutanea tarda and pellagra are examples of endogenous phototoxic dermatoses. Exogenous drug- or chemical-induced photodermatitis manifests either as phototoxicity (a tendency for the individual to sunburn more easily than expected) or as photoallergy (a true immunologic reaction that presents with dermatitis). Drug-induced phototoxicity is triggered by UVA. Contact photosensitivity may occur with plants, perfumes, and sunscreens. The sunscreen oxybenzone (a benzophenone) is a common cause of photoallergic dermatitis. Dermatoses that are worsened or aggravated by UV exposure include SLE and dermatomyositis. Three percent of persons with atopic dermatitis, especially middle-aged women, are photosensitive.

Clinical Findings

A. Symptoms and Signs

The acute inflammatory phase of phototoxicity, if severe enough, is accompanied by pain, fever, GI symptoms, malaise, and even prostration. Signs include erythema, edema, and possibly vesiculation and oozing on exposed surfaces. Peeling of the epidermis and pigmentary changes often result. The key to diagnosis is localization of the rash to photoexposed areas, though eruptions may become

generalized with time to involve photoprotected areas. The lower lip may be affected.

B. Laboratory Findings

Blood and urine tests are generally not helpful unless porphyria cutanea tarda is suggested by the presence of blistering, scarring, milia (white cysts 1–2 mm in diameter) and skin fragility of the dorsal hands, and facial hypertrichosis. Eosinophilia may be present in chronic photoallergic responses.

Differential Diagnosis

The differential diagnosis is long. If a clear history of the use of a topical or systemic photosensitizer is not available and if the eruption is persistent, then a workup including biopsy and light testing may be required. Photodermatitis must be differentiated from contact dermatitis that may develop from one of the many substances in sunscreens, as these may often have a similar distribution. Sensitivity to actinic rays may also be part of a more serious condition, such as porphyria cutanea tarda or lupus erythematosus. These disorders are diagnosed by appropriate blood or urine tests. The most common medications causing a phototoxic reaction are vemurafenib, NSAIDs, voriconazole, tetracyclines, quinolones, hydrochlorothiazide, amiodarone, and chlorpromazine. Other potent photosensitizers include TMP/SMZ, quinine or quinidine, griseofulvin, eculizumab, topical and systemic retinoids (tretinoin, isotretinoin, acitretin), and calcium channel blockers. Polymorphous light eruption (PMLE) is a common idiopathic photodermatitis and often has its onset in the third to fourth decades, except in Native Americans and Latinos, in whom it may present in childhood. PMLE is chronic in nature. Transitory periods of spontaneous remission do occur.

Complications

Some individuals continue to chronically react to light even when they no longer exposed to photosensitizing medications.

Prevention

While sunscreens are useful agents in general and should be used by persons with photosensitivity, patients may react to such low amounts of energy that sunscreens alone may not be sufficient. Sunscreens with an SPF of 30–60 and broad UVA coverage, containing dicamphor sulfonic acid (Mexoryl SX), avobenzone (Parasol 1789), titanium dioxide, and micronized zinc oxide, are especially useful in patients with photoallergic dermatitis. Photosensitivity due to porphyria is not prevented by sunscreens and requires barrier protection (clothing) to prevent outbreaks.

Treatment

A. Specific Measures

Medications should be suspected in cases of photosensitivity even if the particular medication (such as hydrochlorothiazide) has been used for months.

B. Local Measures

When the eruption is vesicular or weepy, treatment is similar to that of any acute dermatitis, using cooling and soothing wet dressings.

Sunscreens should be used as described above. Mid-potency to high-potency topical corticosteroids are of limited benefit in phototoxic reactions but may help in PMLE and photoallergic reactions. Since the face is often involved, close monitoring for corticosteroid side effects is recommended.

C. Systemic Measures

Aspirin may have some value for fever and pain of acute sunburn. Systemic corticosteroids in doses as described for acute contact dermatitis may be required for severe acute photosensitivity reactions. Otherwise, different photodermatoses are treated in specific ways.

Patients with chronic primary photodermatoses may require systemic treatment with hydroxycholoroquine (5 mg/kg once daily) or immunosuppressives, such as azathioprine (50–300 mg once daily) or cyclosporine (3–5 mg/kg once daily).

Prognosis

The most common phototoxic sunburn reactions are usually benign and self-limited. PMLE and some cases of photoallergy can persist for years.

Blakely KM et al. Drug-induced photosensitivity—an update: culprit drugs, prevention and management. Drug Saf. 2019;42:827. [PMID: 30888626]
Hinton AN et al. Feeling the burn: phototoxicity and photoallergy. Dermatol Clin. 2020;38:165. [PMID: 31753189]
Hofmann GA et al. Drug-induced photosensitivity: culprit drugs, potential mechanisms and clinical consequences. J Dtsch Dermatol Ges. 2021;19:19. [PMID: 33491908]

DRUG ERUPTION (Dermatitis Medicamentosa)

ESSENTIALS OF DIAGNOSIS

- Usually, abrupt onset of widespread, symmetric erythematous eruption.
- May mimic any inflammatory skin condition.
- Constitutional symptoms (malaise, arthralgia, headache, and fever) may be present.

General Considerations

Rashes are among the most common adverse reactions to medications and occur in 2–3% of hospitalized patients. There are multiple different types of cutaneous reactions to medications. Penicillins, cephalosporins, and NSAIDs are the most common cause of urticarial drug eruptions.

Antibiotics, anticonvulsants, allopurinol, and NSAIDs are common causes of maculopapular or morbilliform reactions. Drug-induced hypersensitivity reaction (DIHS) (also known as drug eruption with eosinophilia and systemic symptoms [DRESS]) is most often caused by anticonvulsants, allopurinol, and sulfonamides. SJS and TEN most commonly occur in response to antibiotics, sulfonamides, anticonvulsants, allopurinol, and NSAIDs. Phenolphthalein, pyrazolone derivatives, tetracyclines, NSAIDs, TMP-SMZ, and barbiturates are the major causes of fixed drug eruptions. Calcium channel blockers are a common cause of pruritus and eczemas in older adults.

Certain genetic polymorphisms of antigen-presenting major histocompatibility (MHC) loci increase the risk for the development of severe drug eruptions, including SJS/TEN and DIHS. Pharmacogenetic testing can help predict who is at risk for and therefore should avoid certain medication exposures.

Clinical Findings

A. Symptoms and Signs

Drug eruptions are generally classified as "simple" or "complex," referring to the risk of morbidity and mortality associated with the specific eruption. Simple morbilliform or maculopapular drug eruptions involve an exanthem, usually appear in the second week of medication therapy, and have no associated constitutional symptoms or abnormal laboratory findings. Complex drug eruptions include DIHS and SJS/TEN.

DIHS occurs later than the simple morbilliform drug eruptions with signs and symptoms developing 2–6 weeks after the medication has been started and has associated constitutional symptoms and abnormal laboratory findings. These may include fevers, chills, hematologic abnormalities (especially eosinophilia and atypical lymphocytosis), and abnormal liver or kidney function. Coexistent reactivation of certain viruses, especially HHV-6, but also Epstein-Barr virus, cytomegalovirus, HHV-7, and parvovirus B19, may be present and may be important in the pathogenesis of these complex drug eruptions. Table 6–3 summarizes the types of skin reactions, their appearance and distribution, and the common offenders in each case.

B. Laboratory Findings

Routinely ordered blood work is of no value in the diagnosis of simple drug eruptions, except upon initial evaluation to ensure that there is no systemic involvement. In complex drug eruptions, the CBC, liver biochemical tests, and kidney function tests should be monitored. Skin biopsies may be helpful in making the diagnosis. Serum PCR for HHV-6, HHV-7, Epstein-Barr virus, cytomegalovirus, and parvovirus B19 is performed in some centers.

Differential Diagnosis

Observation after discontinuation, which may be a slow process, helps establish the diagnosis. Rechallenge, though of theoretical value, may pose a danger to the patient and is best avoided.

Complications

Some cutaneous drug reactions may be associated with visceral involvement. The organ systems involved depend on the individual medication or drug class. Most common is an infectious mononucleosis-like illness and hepatitis associated with administration of anticonvulsants. Myocarditis may be a serious complication of drug-induced hypersensitivity syndrome and may present acutely or months after initial rash onset. Months after recovering from DIHS, patients may suffer hypothyroidism.

Treatment

A. General Measures

Systemic manifestations are treated as they arise (eg, anemia, icterus, purpura). Antihistamines may be of value in urticarial and angioneurotic reactions. Epinephrine 1:1000, 0.5–1 mL intravenously or subcutaneously, should be used as an emergency measure. In DIHS, corticosteroids are typically required; the most common regimen is oral prednisone, 1–1.5 mg/kg/day tapering slowly over a minimum of 6 weeks, since rapid taper leads to rebound and more recalcitrant disease. In the case of allopurinol-induced DIHS, starting a steroid-sparing agent (eg, mycophenolate mofetil) at the time of prednisone initiation is recommended because allopurinol-induced DIHS tends to rebound after corticosteroid discontinuation. Treatment in this special case often takes up to 12 months.

B. Local Measures

SJS/TEN with extensive blistering eruptions resulting in erosions and superficial ulcerations demands hospitalization and nursing care as for burn patients. See Erythema Multiforme/Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, above.

Prognosis

Drug rash usually disappears upon withdrawal of the medication and proper treatment. DIHS may be associated with autoimmune phenomena, including abnormal thyroid function. This can occur months after the hypersensitivity syndrome has resolved.

Cheraghlou S et al. Fixed drug eruptions, bullous drug eruptions, and lichenoid drug eruptions. Clin Dermatol. 2020;38:679. [PMID: 33341201]

Mockenhaupt M. Bullous drug reactions. Acta Derm Venereol. 2020;100:adv00057. [PMID: 32039459]

Noe MH et al. Diagnosis and management of Stevens-Johnson syndrome/toxic epidermal necrolysis. Clin Dermatol. 2020;38:607. [PMID: 33341195]

Owen CE et al. Recognition and management of severe cutaneous adverse drug reactions (including drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, and toxic epidermal necrolysis). Med Clin North Am. 2021;105:577. [PMID: 34059239]

Table 6–3. Skin reactions due to systemic medications.

Reaction	Appearance	Distribution and Comments	Common Offenders
Allergic vasculitis	The primary lesion is typically a 2–3 mm purpuric papule. Other morphologies include urticaria that lasts over 24 hours, vesicles, bullae, or necrotic ulcers.	Most severe on the legs.	Sulfonamides, phenytoin, propylthiouracil.
Drug exanthem	Morbilliform, maculopapular, exanthematous reactions.	The most common skin reaction to medications. Initially begins on trunk 7–10 days after the medication has been started. Spreads to extremities and begins to clear on the trunk over 3–5 days. In previously exposed patients, the rash may start in 2–3 days. Fever may be present.	Antibiotics (especially ampicillin and TMP-SMZ), sulfonamides and related compounds (including thiazide diuretics, furosemide, and sulfonylurea hypoglycemic agents), and barbiturates.
Drug-related subacute cutaneous lupus erythematosus (Drug-induced SLE rarely produces a skin reaction)	May present with a photosensitive rash, annular lesions, or psoriasis on upper trunk.	Less severe than SLE, sparing the kidneys and CNS. Recovery often follows medication withdrawal.	Diltiazem, etanercept, hydrochlorothiazide, infliximab, lisinopril, terbinafine.
Erythema nodosum	Inflammatory cutaneous nodules.	Usually limited to the extensor aspects of the legs. May be accompanied by fever, arthralgias, and pain.	Oral contraceptives.
Drug-induced hypersensitivity syndrome	Erythroderma	Entire skin surface. Typically associated with elevated liver biochemical tests, eosinophilia, and AKI. Eruption begins between 2 and 6 weeks after first dose of medication.	Allopurinol, sulfonamides, aromatic anticonvulsants, NSAID, dapsone, lamotrigine.
Fixed drug eruptions	Single or multiple demarcated, round, erythematous plaques that often become hyperpigmented.	Recur at the same site when the medication is repeated. Hyperpigmentation, if present, remains after healing.	Antimicrobials, analgesics (acetaminophen, ibuprofen, and naproxen), barbiturates, heavy metals, antiparasitic agents, antihistamines, phenolphthalein.
Lichenoid and lichen planus–like eruptions	Pruritic, erythematous to violaceous polygonal papules that coalesce or expand to form plaques.	May be in photo- or nonphotodistributed pattern.	Carbamazepine, furosemide, hydroxychloroquine, phenothiazines, beta-blockers, quinidine, quinine, sulfonylureas, tetracyclines, thiazides, and triprolidine.
Photosensitivity: increased sensitivity to light, often of UVA wavelengths, but may be due to UVB or visible light as well	Sunburn, vesicles, papules in photodistributed pattern.	Exposed skin of the face, the neck, and the backs of the hands and, in women, the lower legs. Exaggerated response to UV light.	Sulfonamides and sulfonamide-related compounds (thiazide diuretics, furosemide, sulfonylureas), tetracyclines, phenothiazines, sulindac, amiodarone, voriconazole, and NSAIDs.
Pigmentary changes	Flat hyperpigmented areas.	Forehead and cheeks (chloasma, melasma). The most common pigmentary disorder associated with drug ingestion. Improvement is slow despite stopping the medication.	Oral contraceptives are the usual cause. Diltiazem causes facial hyperpigmentation that may be difficult to distinguish from melasma.
	Blue-gray discoloration.	Light-exposed areas.	Chlorpromazine and related phenothiazines.

(*continued*)

Table 6–3. Skin reactions due to systemic medications. (continued)

Reaction	Appearance	Distribution and Comments	Common Offenders
	Brown or blue-gray pigmentation.	Generalized.	Heavy metals (silver, gold, bismuth, and arsenic).
	Blue-black patches on the shins.		Minocycline, chloroquine.
	Blue-black pigmentation of the nails and palate and depigmentation of the hair.		Chloroquine.
	Slate-gray color.	Primarily in photoexposed areas.	Amiodarone.
	Brown discoloration of the nails.	Especially in more darkly pigmented patients.	Hydroxyurea.
Pityriasis rosea–like eruptions	Oval, red, slightly raised patches with central scale.	Mainly on the trunk.	Barbiturates, bismuth, captopril, clonidine, methopromazine, metoprolol, metronidazole, and tripelennamine.
Psoriasiform eruptions	Scaly red plaques.	May be located on trunk and extremities. Palms and soles may be hyperkeratotic. May cause psoriasiform eruption or worsen psoriasis.	Antimalarials, lithium, beta-blockers, and TNF inhibitors.
SJS/TEN	Target-like lesions. Bullae may occur. Mucosal involvement.	Usually trunk and proximal extremities.	Sulfonamides, anticonvulsants, allopurinol, NSAIDs, lamotrigine.
Urticaria	Red, itchy wheals that vary in size from < 1 cm to many centimeters. May be accompanied by angioedema.	Chronic urticaria is rarely caused by medications.	Acute urticaria: penicillins, NSAIDs, sulfonamides, opioids, and salicylates. Angioedema is common in patients receiving ACE inhibitors and ARBs.

SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; TMP-SMZ, trimethoprim-sulfamethoxazole; TNF, tumor necrosis factor.

MISCELLANEOUS[1]

PRURITUS

Pruritus is the sensation that provokes a desire to scratch. Pruritus as a medical complaint is 40% as common as low back pain. Elderly Asian men are most significantly affected, with 20% of all health care visits in Asian men over the age of 65 involving the complaint of itch. The quality of life of a patient with chronic pruritus is the same as a patient undergoing hemodialysis. Better understanding of the role of pruritogens (interleukins-31, -4, -13 and thymic stromal lymphopoietin) in the pathophysiology of itch has enabled recent therapeutic advances.

Dry skin is the first cause of itch that should be sought since it is common and easily treated. The next step is to determine whether a primary skin lesion with associated pruritus is present. Examples of primary cutaneous pruritic diseases include scabies, atopic dermatitis, insect bites, pediculosis, contact dermatitis, drug reactions, urticaria, psoriasis, lichen planus, and fiberglass dermatitis, all of which have recognizable morphologies. The treatment of an underlying primary skin condition usually results in control of the associated pruritus.

Persistent pruritus not explained by cutaneous disease or association with a primary skin eruption should prompt a staged workup for systemic causes. Common causes of pruritus associated with systemic diseases include endocrine disorders (eg, hypo- or hyperthyroidism or hyperparathyroidism), psychiatric disturbances, lymphoma, leukemia, internal malignant disorders, iron deficiency anemia, HIV, hypercalcemia, cholestasis, and some neurologic disorders. Calcium channel blockers can cause pruritus with or without eczema, even years after they have been started, and it may take up to 1 year for pruritus to resolve after the calcium channel blocker has been stopped.

Treatment

The treatment of chronic pruritus can be frustrating. Most cases of pruritus are not mediated by histamine, hence the poor response of many patients to antihistamines. Emollients for dry skin are listed in Table 6–2. Emollient creams (preferred over lotions) should be generously applied from neck to toe immediately after towel drying and again one more time per day. Neuropathic pruritus responds to neurally acting agents, such as gabapentin (starting at 300 mg orally at around 4 PM and a second dose of 600 mg orally at bedtime) or pregabalin (150 mg orally daily).

[1]Hirsutism is discussed in Chapter 26.

Combinations of antihistamines, sinequan, gabapentin, pregabalin, mirtazapine, and opioid antagonists can be attempted in refractory cases. In cancer-associated and other forms of pruritus, aprepitant 80 mg orally daily for several days can be dramatically effective. Pruritus in conjunction with uremia and hemodialysis and to a lesser degree the pruritus of liver disease may be helped by phototherapy with UVB or PUVA. Gabapentin or mirtazapine may relieve the pruritus of CKD. Current trials are underway to study the inhibition of Il-31 (nemolizumab), Il-4 (dupilumab), IL-13 JAK (tofacitinib), opioid receptor, neurokinin, phosphodiesterase-4, and thymic stromal lymphopoietin in the treatment of chronic pruritus.

Prognosis

Elimination of external factors and irritating agents may give complete relief. Pruritus accompanying a specific skin disease will subside when the skin disease is controlled. Pruritus accompanying serious internal disease may not respond to any type of therapy.

Avila C et al. Cannabinoids for the treatment of chronic pruritus: a review. J Am Acad Dermatol. 2020;82:1205. [PMID: 31987788]
Kabashima K et al; Nemolizumab-JP01 Study Group. Trial of nemolizumab and topical agents for atopic dermatitis with pruritus. N Engl J Med. 2020;383:141. [PMID: 32640132]
Misery L et al. Chronic itch: emerging treatments following new research concepts. Br J Pharmacol. 2021;178:4775. [PMID: 34463358]
Sutaria N et al. Itch: pathogenesis and treatment. J Am Acad Dermatol. 2022;86:17. [PMID: 34648873]

Anogenital Pruritus

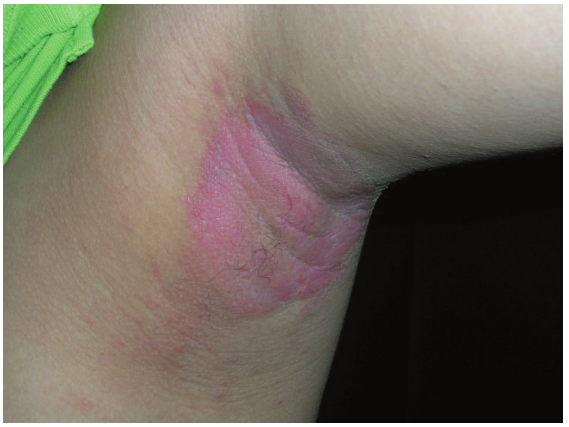
ESSENTIALS OF DIAGNOSIS

- Anogenital itching, chiefly nocturnal.
- Skin findings are highly variable, ranging from none to excoriations and inflammation of any degree, including lichenification.

General Considerations

Anogenital pruritus may be due to a primary inflammatory skin disease (intertrigo, psoriasis, lichen simplex chronicus, seborrheic dermatitis, lichen sclerosus), contact dermatitis (soaps, wipes, colognes, douches, and topical treatments), irritating secretions (diarrhea, leukorrhea, or trichomoniasis), infections (candidiasis, dermatophytosis, erythrasma), or oxyuriasis (pinworms). Erythrasma (Figure 6–36) is diagnosed by coral-red fluorescence with Wood light and cured with erythromycin. Squamous cell carcinoma of the anus and extramammary Paget disease are rare causes of genital pruritus.

In pruritus ani, hemorrhoids are often found, and leakage of mucus and bacteria from the distal rectum onto the perianal skin may be important in cases in which no other skin abnormality is found.



▲ **Figure 6–36. Erythrasma of the axilla.** (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Many women experience pruritus vulvae. Pruritus vulvae does not usually involve the anal area, though anal itching may spread to the vulva. In men, pruritus of the scrotum is most commonly seen in the absence of pruritus ani.

Up to one-third of unidentified causes of anogenital pruritus may be due to nerve impingements of the lumbosacral spine, so evaluation of lumbosacral spine disease is appropriate if no skin disorder is identified and topical therapy is ineffective.

Clinical Findings

A. Symptoms and Signs

The only symptom is itching. Physical findings are usually not present, but there may be erythema, fissuring, maceration, lichenification, excoriations, or changes suggestive of candidiasis or tinea.

B. Laboratory Findings

Microscopic examination or culture of tissue scrapings may reveal yeasts or fungi. Stool examination may show pinworms. Radiologic studies may demonstrate lumbarsacral spinal disease.

Differential Diagnosis

The etiologic differential diagnosis consists of *Candida* infection, parasitosis, local irritation from contactants or irritants, nerve impingement, and other primary skin disorders of the genital area, such as psoriasis, seborrhea, intertrigo, or lichen sclerosus.

Prevention

Instruct the patient in proper anogenital hygiene after treating systemic or local conditions.

Treatment

Treating constipation, preferably with high-fiber management (psyllium), may help. Instruct the patient to use very

soft or moistened tissue or cotton after bowel movements and to clean the perianal area thoroughly with cool water if possible. Women should use similar precautions after urinating. Patch testing reveals clinically relevant allergy in about 20% of patients, often to methylchloroisothiazolinone or methylisothiazolinone, preservatives commonly found in "baby wipes" and other personal care products.

Pramoxine cream or lotion or hydrocortisone-pramoxine (Pramosone), 1% or 2.5% cream, lotion, or ointment, is helpful for anogenital pruritus and should be applied after a bowel movement. Topical doxepin cream 5% is similarly effective but may be sedating. Topical calcineurin inhibitors (tacrolimus 0.03%) improve pruritus ani in patients with atopic dermatitis. Underclothing should be changed daily, and in men, the seam of their "boxers" should not rub against or contact the scrotum. Balneol Perianal Cleansing Lotion or Tucks premoistened pads, ointment, or cream may be very useful for pruritus ani. About one-third of patients with scrotal or anal pruritus will respond to capsaicin cream 0.006%. The use of high-potency topical corticosteroids should be avoided in the genital area.

Prognosis

Although benign, anogenital pruritus is often persistent and recurrent.

Cohee MW et al. Benign anorectal conditions: evaluation and management. Am Fam Physician. 2020;101:24. [PMID: 31894930]

Raef HS et al. Vulvar pruritus: a review of clinical associations, pathophysiology and therapeutic management. Front Med (Lausanne). 2021;8:649402. [PMID: 33898486]

ULCERS

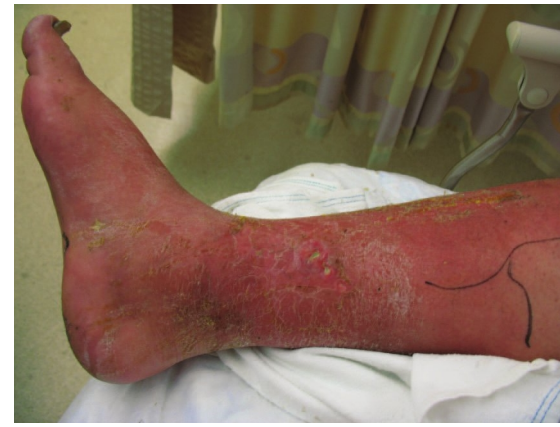
Leg Ulcers Secondary to Venous Insufficiency

ESSENTIALS OF DIAGNOSIS

- History of varicosities, thrombophlebitis, or postphlebitic syndrome.
- Irregular ulceration, often on the medial lower legs above the malleolus.
- Edema of the legs, varicosities, hyperpigmentation, red and scaly areas (stasis dermatitis), and scars from old ulcers support the diagnosis.

General Considerations

Patients at risk may have a history of venous insufficiency, family history, varicosities, obesity, or genetic diseases that predispose to venous insufficiency (see Chronic Venous Insufficiency, Chapter 12). The left leg is usually more severely affected than the right.



▲ **Figure 6–37.** Venous stasis ulcer. (Used, with permission, from Lindy Fox, MD.)

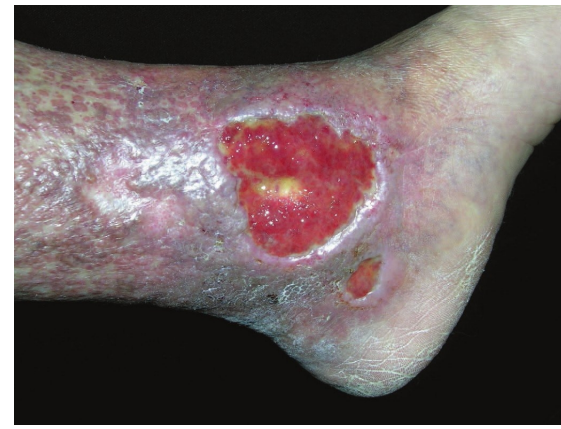
Clinical Findings

A. Symptoms and Signs

Classically, chronic edema is followed by a dermatitis, which is often pruritic. These changes are followed by hyperpigmentation, skin breakdown, and eventually sclerosis of the skin of the lower leg (Figure 6–37). Red, pruritic patches of stasis dermatitis often precede ulceration (Figure 12–2). The ulcer base may be clean, but it often has a yellow fibrin eschar that may require surgical removal (Figure 6–38). Ulcers that appear on the feet, toes, or above the knees should be approached with other diagnoses in mind.

B. Laboratory Findings

Because venous insufficiency plays a role in 75–90% of lower leg ulcerations, testing of venous competence is a required part of a leg ulcer evaluation even without



▲ **Figure 6–38.** Ulcer—venous stasis ulcer. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

changes of venous insufficiency (see Chapter 12). Doppler examination is usually sufficient (except in the diabetic patient) to evaluate venous competence. Arterial insufficiency may coexist with venous disease. An ankle/brachial index (ABI) less than 0.7 indicates the presence of significant arterial disease and requires vascular surgery consultation.

Differential Diagnosis

The differential includes vasculitis, pyoderma gangrenosum, arterial ulcerations, infection, trauma, skin cancer, arachnid bites, and sickle cell anemia. When the diagnosis is in doubt, a punch biopsy from the border (not base) of the lesion may be helpful.

Prevention

Compression stockings to reduce edema are the most important means of prevention. Compression should achieve a pressure of 30 mm Hg below the knee and 40 mm Hg at the ankle. The stockings should not be used in patients with arterial insufficiency with an ABI less than 0.7. Pneumatic sequential compression devices may be of great benefit when edema is refractory to standard compression dressings.

Treatment

A. Local Measures

Clean the base of the ulcer with saline or cleansers, such as Saf-Clens®. A curette or small scissors can be used to remove the yellow fibrin eschar; local anesthesia may be used if the areas are very tender.

Overall, there is little evidence to support topical antibiotics for the treatment of venous insufficiency ulcerations. Metronidazole gel is used to reduce bacterial growth and odor. Silver impregnated dressings may aid in healing. Red dermatitic skin is treated with a medium- to high-potency corticosteroid ointment such as triamcinolone acetonide 0.1% ointment. The ulcer is then covered with an occlusive hydroactive dressing (DuoDerm® or Cutinova®) or a polyurethane foam (Allevyn) followed by an Unna zinc paste boot. This is changed weekly. The ulcer should begin to heal within weeks, and healing should be complete within 4–6 months. If the patient has no history of skin cancer in the area, becaplermin (Regranex) may be applied to ulcers that are not becoming smaller or developing a granulating base. Some ulcerations require skin grafting.

No topical intervention has evidence to suggest that it will improve healing of arterial leg ulcers.

B. Systemic Therapy

Pentoxifylline, 400 mg orally three times daily administered with compression dressings, is beneficial in accelerating healing of venous insufficiency leg ulcers. Zinc supplementation is occasionally beneficial in patients with low serum zinc levels.

In the absence of cellulitis, there is no role for systemic antibiotics in the treatment of venous insufficiency ulcers. The diagnosis of cellulitis in the setting of a venous insufficiency ulcer can be very difficult. Surface cultures are of limited value. Cellulitis should be considered in the following settings: (1) expanding warmth and erythema surrounding the ulceration, with or without (2) increasing pain of the ulceration. The patient may also report increased exudate from the ulceration, but this without the other cardinal findings of cellulitis does not confirm the diagnosis of cellulitis. If cellulitis accompanies the ulcer, oral antibiotics are recommended: dicloxacillin, 250 mg four times a day, or levofloxacin, 500 mg once daily for 1–2 weeks, is usually adequate. Routine use of antibiotics and treating bacteria isolated from a chronic ulcer without clinical evidence of infection is discouraged. If the ulcer fails to heal or there is a persistent draining tract in the ulcer, underlying osteomyelitis should be sought.

Prognosis

The combination of limited debridement, compression dressings or stockings, and moist dressings will heal the majority of venous stasis ulcers within an average of 18 months. These modalities need to be applied at least 80% of the time to optimize ulcer healing. Topical growth factors, antibiotics, debriding agents, and xenografts and autografts can be considered in recalcitrant cases but are not required in most patients. Exercise in combination with compression therapy has an adjuvant role in promoting the healing of venous ulcerations. The failure of venous insufficiency ulcerations to heal is most often related to inconsistent use of basic treatment methods. Ongoing control of edema is essential to prevent recurrent ulceration. The use of compression stockings following ulcer healing is critical to prevent recurrence, with recurrence rates 2–20 times higher if patients do not comply with compression stocking use. Patients with an ABI below 0.5 or refractory ulcerations (or both) should be considered for surgical procedure (artery-opening procedures or ablation of the incompetent superficial vein). Early endovenous ablation has been shown to improve healing in patients with venous insufficiency ulcers.

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PIGMENTARY DISORDERS

Although the color of skin may be altered by many diseases and agents, the vast majority of patients have either an increase or decrease in pigment secondary to an inflammatory disease, such as acne or atopic dermatitis.

Other pigmentary disorders include those resulting from exposure to exogenous pigments, such as carotenemia, argyria, and tattooing. Other endogenous pigmentary disorders are attributable to metabolic substances (eg, hemosiderin [iron]) in purpuric processes, to homogentisic acid in ochronosis, and bile pigments.

Classification

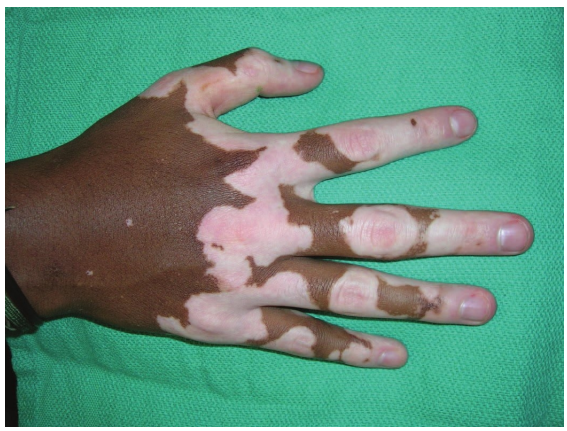
Disorders of hyper- or hypopigmentation may be considered to be primary or secondary to other disorders. Depigmentation, the absence of all pigment, should be differentiated from hypopigmentation, in which the affected skin is lighter than baseline skin color, but not completely devoid of pigment.

The evaluation of pigmentary disorders is helped by Wood light, which accentuates epidermal pigmentation in hyperpigmented disorders and highlights complete loss of pigment in depigmentating disorders. Depigmentation, as seen in vitiligo, enhances with Wood light examination, whereas postinflammatory hypopigmentation does not.

A. Primary Pigmentary Disorders

1. Hyperpigmentation—The disorders in this category are nevoid, congenital, or acquired. Nevoid and congenital disorders include pigmented nevi, mosaic hyperpigmentation, ephelides (juvenile freckles), and lentigines (senile freckles). Hyperpigmentation due to systemic diseases may be seen in in association with Addison disease, vitamin B_{12} deficiency, hemochromatosis, and Wilson disease. Melasma (chloasma) occurs as patterned hyperpigmentation of the face, most commonly as a direct effect of estrogens. It may occur during pregnancy, exposure to oral contraceptives, or be idiopathic. Although more common in women, melasma affects both sexes and all races.

2. Hypopigmentation and depigmentation—Depigmenting disorders in this category are vitiligo, albinism, and piebaldism. In vitiligo, pigment cells (melanocytes) are destroyed (Figure 6–39). Vitiligo, present in approximately 1% of the population, may be associated with other autoimmune disorders, such as autoimmune thyroid disease, pernicious anemia, diabetes mellitus, and Addison disease.



▲ **Figure 6–39.** Depigmented—vitiligo. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

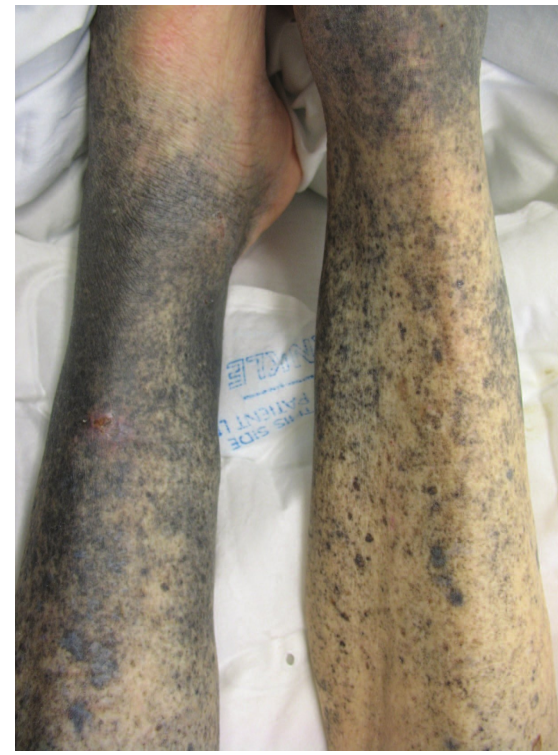
B. Secondary Pigmentary Disorders

Any damage to the skin (irritation, allergy, infection, excoriation, burns, or dermatologic therapy, such as chemical peels and freezing with liquid nitrogen) may result in hyper- or hypopigmentation. Several disorders of clinical importance are described below.

1. Hyperpigmentation—The most common type of secondary hyperpigmentation occurs after another inflammatory dermatologic condition, such as acne, lichen planus, or eczema, and is most commonly seen in moderately complexioned persons (Asian, Latinx, and light-skinned Black individuals). It is called post-inflammatory hyperpigmentation. Hemosiderin deposition, as in stasis dermatitis, may lead to hyperpigmentation that is red-brown in color.

Pigmentation may be produced by certain medications, eg, chloroquine, chlorpromazine, minocycline (Figure 6–40), and amiodarone. Fixed drug eruptions to phenolphthalein (in laxatives), TMP-SMZ, NSAIDs, and tetracyclines also lead to hyperpigmentation, typically in annular patches.

2. Hypopigmentation—Hypopigmentation may complicate atopic dermatitis, lichen planus, psoriasis, discoid lupus, and lichen simplex chronicus. It may also be posttraumatic or iatrogenic (eg, due to the use of superpotent topical corticosteroids) or both. *Clinicians must exercise special care in using liquid nitrogen on any patients with*



▲ **Figure 6–40.** Minocycline hyperpigmentation. (Used, with permission, from Lindy Fox, MD.)

darker skin tones since doing so may result in hypopigmentation or depigmentation, at times permanent. Intralesional or intra-articular injections of high concentrations of corticosteroids may also cause localized temporary hypopigmentation. Vitiligo is a known complication of immune checkpoint inhibitor therapy for melanoma.

Complications

Actinic keratoses and skin cancers are more likely to develop in persons with vitiligo. Severe emotional trauma may occur in extensive vitiligo and other types of hypo- and hyperpigmentation, particularly in naturally dark-skinned persons.

Treatment & Prognosis

A. Hyperpigmentation

Therapeutic bleaching preparations generally contain hydroquinone. Hydroquinone has occasionally caused unexpected hypo- or hyperpigmentation, or even secondary ochronosis and pigmented milia, particularly with prolonged use.

The role of exposure to UV light cannot be overstressed as a factor promoting or contributing to most disorders of hyperpigmentation, and such exposure should be minimized. Melasma, ephelides, and postinflammatory hyperpigmentation may be treated with varying success with 4% hydroquinone and a sunscreen containing UVA photoprotectants (Avobenzone, Mexoryl, zinc oxide, titanium dioxide). Tretinoin cream, 0.025–0.05%, may be added. Adjuvant topical options for melasma include kojic acid, ascorbic acid, cysteamine, niacinamide, and azelaic acid. Superficial melasma responds well to topical therapy, but if there is predominantly dermal deposition of pigment (does not enhance with Wood light), the prognosis is poor. Response to therapy may take months and requires avoidance of sunlight. Hyperpigmentation often recurs after treatment if the skin is exposed to UV light. Tranexamic acid, 250 mg twice a day for 8–12 weeks, is an oral treatment for melasma. It should not be used in patients with hypercoagulability. Acne with postinflammatory hyperpigmentation responds well to azelaic acid and tretinoin, since both address acne and hyperpigmentation. Solar lentigines respond to liquid nitrogen application. Tretinoin 0.1% cream or tazarotene 0.1% used over 10 months can fade solar lentigines, facial hyperpigmentation, and postinflammatory hyperpigmentation. Lasers are available for the removal of epidermal and dermal pigment and should be considered for patients whose responses to medical treatment are inadequate.

B. Hypopigmentation

In secondary hypopigmentation, repigmentation may occur spontaneously. Cosmetics such as Covermark and Dermablend are highly effective for concealing disfiguring patches. Therapy of vitiligo is long and tedious, and the patient must be strongly motivated. If less than 20% of the skin is involved (most cases), topical tacrolimus 0.1% twice daily is the first-line therapy. A superpotent corticosteroid may also be used, but local skin atrophy from prolonged use may ensue. With 20–25% involvement, narrowband UVB or oral PUVA is the best option. Severe phototoxic response (sunburn) may occur with PUVA. The face and upper chest respond best, and the fingertips and the genital areas do not respond as well to treatment. Years of treatment may be required. Topical or systemic JAK inhibitors (tofactinib, ruxolitinib) may be effective in some patients with recalcitrant vitiligo.

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ALOPECIA

Classification

Alopecias are divided into scarring and nonscarring forms. When evaluating a patient who complains of hair loss, it is most important to determine if follicular markings (the opening where hair exits the skin) are present or absent. Present follicular markings suggest a nonscarring alopecia; absent follicular markings suggest a scarring alopecia.

Nonscarring Alopecia

Nonscarring alopecia may occur in association with various systemic diseases, such as SLE, secondary syphilis, hyper- or hypothyroidism, iron deficiency anemia, vitamin D deficiency, and pituitary insufficiency. Prompt and adequate control of the underlying disorder usually leads to hair regrowth. Specific types of nonscarring alopecia are described below.

Androgenetic alopecia, the most common form of alopecia, is of genetic predetermination. In men, the earliest changes occur at the anterior portions of the calvarium on either side of the "widow's peak" and on the crown (vertex). The extent of hair loss is variable and unpredictable. Minoxidil 5% is available over the counter and can be recommended for persons with recent onset (less than 5 years) and smaller areas of alopecia. Approximately 40% of patients treated twice daily for a year will have moderate to dense growth. Finasteride (Propecia), 1 mg orally daily, has similar efficacy and may be additive to minoxidil.

Androgenetic alopecia also occurs in women. Classically, there is retention of the anterior hairline while there is diffuse thinning of the vertex scalp hair and a widening of the part. Treatment includes topical minoxidil (5% once daily) and, in women not of childbearing potential, finasteride at doses up to 2.5 mg/day orally. Spironolactone

50–200 mg daily may be used in premenopausal women. Low-dose oral minoxidil (0.25–1 mg daily in women and 2.5–5 mg daily in men) is also safe and effective. A workup consisting of determination of serum testosterone, DHEAS, iron, total iron-binding capacity, thyroid function tests, vitamin D level, and a CBC will identify most other causes of hair thinning in premenopausal women. Women who complain of thin hair but show little evidence of alopecia need follow-up, because more than 50% of the scalp hair can be lost before the clinician can perceive it.

Telogen effluvium is a transitory increase in the number of hairs in the telogen (resting) phase of the hair growth cycle. This may occur spontaneously; appear at the termination of pregnancy; be precipitated by severe illness, "crash dieting," high fever, stress from surgery, shock, malnutrition, or iron deficiency; or be provoked by hormonal contraceptives. Whatever the cause, telogen effluvium usually has a latent period of 4 months. The prognosis is generally good. The condition is diagnosed by the presence of large numbers of hairs with white bulbs coming out upon gentle tugging of the hair. Counts of hairs lost by the patient on combing or shampooing often exceed 150 per day, compared to an average of 70–100. If iron deficiency is suspected, a serum ferritin should be obtained, and any value less than 40 ng/mL followed with supplementation.

Alopecia areata is of unknown cause but is believed to be an immunologic process. Typically, there are patches that are perfectly smooth and without scarring. Tiny hairs 2–3 mm in length, called "exclamation hairs," may be seen. Telogen hairs are easily dislodged from the periphery of active lesions. The beard, brows, and lashes may be involved. Involvement may extend to all of the scalp hair (**alopecia totalis**) or to all scalp and body hair (**alopecia universalis**). Severe forms may be treated by systemic corticosteroid therapy, although recurrences follow discontinuation of therapy. Alopecia areata is occasionally associated with autoimmune disorders, including Hashimoto thyroiditis, pernicious anemia, Addison disease, and vitiligo. Additional comorbidities may include SLE, atopy, and mental health disease.

Intralesional corticosteroids are frequently effective for alopecia areata. Triamcinolone acetonide in a concentration of 2.5–10 mg/mL is injected in aliquots of 0.1 mL at approximately 1- to 2-cm intervals, not exceeding a total dose of 30 mg per month for adults. Alopecia areata is usually self-limiting, with complete regrowth of hair in 80% of patients with focal disease. Some mild cases are resistant to treatment, as are the extensive totalis and universalis types. Support groups for patients with extensive alopecia areata are beneficial. Oral JAK inhibitors (ruxolitinib, tofacitinib) are therapeutic options for patients with highly morbid disease, although relapse is the rule once the medication has been stopped. Efficacy of topical JAK inhibitors for alopecia areata is under investigation.

In **trichotillomania** (the pulling out of one's own hair), the patches of hair loss are irregular, with short, growing hairs almost always present, since they cannot be pulled out until they are long enough. The patches are often unilateral, occurring on the same side as the patient's dominant hand. The patient may be unaware of the habit. *N*-acetylcysteine (1200–2400 mg orally per day for 12 weeks) may be effective.

Scarring (Cicatricial) Alopecia

Cicatricial alopecia may occur following any type of trauma or inflammation that may scar hair follicles. Examples include chemical or physical trauma, bacterial or fungal infections, severe herpes zoster, chronic discoid lupus erythematosus (DLE), systemic sclerosis (scleroderma), and excessive ionizing radiation. The specific cause is often suggested by the history, the distribution of hair loss, and the appearance of the skin, as in DLE. Specific dermatologic diseases of the scalp that result in scarring alopecia include lichen planopilaris, frontal fibrosing alopecia, dissecting cellulitis of the scalp, and folliculitis decalvans. Biopsy is useful in the diagnosis of scarring alopecia, but specimens must be taken from the active border and not from the scarred central zone. Scarring alopecias are irreversible and permanent. It is important to diagnose and treat the scarring process as early in its course as possible.

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NAIL DISORDERS

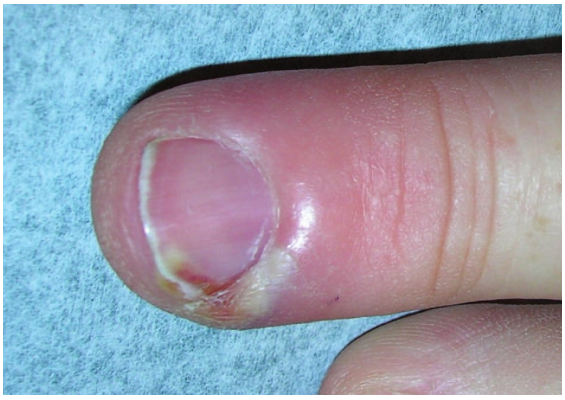
1. Morphologic Nail Abnormalities

Classification

Acquired nail disorders may be classified as local or associated with systemic or generalized skin diseases.

A. Local Nail Disorders

1. Onycholysis (distal separation of the nail plate from the nail bed, usually of the fingers) is caused by excessive exposure to water, soaps, detergents, alkalies, and industrial cleaning agents. Candidal infection of the nail folds and subungual area, nail hardeners, drug-induced photosensitivity, hyper- or hypothyroidism, and psoriasis may cause onycholysis.
2. Distortion of the nail, including nail splitting, occurs as a result of chronic inflammation or infiltration of the nail matrix underlying the eponychial fold.



▲ **Figure 6–41. Acute paronychia.** (Used, with permission, from E.J. Mayeaux Jr, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

Such changes may be caused by impingement on the nail matrix by inflammatory diseases (eg, psoriasis, lichen planus, eczema), warts, tumors, or cysts.

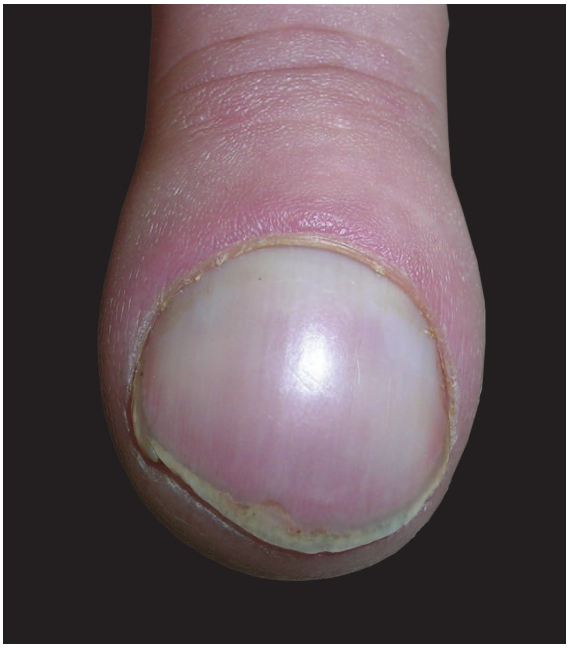
3. Discoloration and crumbly thickened nails are noted in dermatophyte infection and psoriasis.
4. Allergic reactions (to resins in undercoats and polishes or to nail glues) are characterized by onycholysis or by grossly distorted, hypertrophic, and misshapen nails.
5. Paronychia is inflammation of the lateral or proximal nail folds. Acute paronychia presents as a painful erythematous papulonodule or frank abscess of the nail fold and is most commonly due to infection with *S aureus* (Figure 6–41). Chronic paronychia is most often caused by irritation from water or chemicals with resultant inflammation and possible *Candida* superinfection.

B. Nail Changes Associated with Systemic or Generalized Skin Diseases

1. Beau lines (transverse furrows) affect all nails and classically develop after a serious systemic illness.
2. Atrophy of the nails may be related to trauma or to vascular or neurologic disease.
3. Clubbed fingers may be due to the prolonged hypoxemia associated with cardiopulmonary disorders (Figure 6–42) (see Chapter 9).
4. Spoon nails may be seen in anemic patients.
5. Stippling or pitting of the nails is seen in psoriasis, alopecia areata, and hand eczema (Figure 6–23).
6. Nail hyperpigmentation may be caused by many chemotherapeutic agents, but especially the taxanes.

Differential Diagnosis

Onychomycosis may cause nail changes identical to those seen in psoriasis. Careful examination for more characteristic lesions elsewhere on the body is essential to the diagnosis of the nail disorders. Cancer should be suspected (eg, Bowen disease or squamous cell carcinoma) as the cause of any persistent solitary subungual or periungual lesion.



▲ **Figure 6–42. Clubbing of the finger in a 31-year-old man with congenital heart disease. Note the thickening around the proximal nail folds.** (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. The Color Atlas of Family Medicine, 3rd ed. McGraw-Hill, 2019.)

Complications

Toenail changes may lead to an ingrown nail—in turn often complicated by bacterial infection and occasionally by exuberant granulation tissue. Poor manicuring and poorly fitting shoes may contribute to this complication. Cellulitis may result.

Treatment & Prognosis

Treatment consists usually of careful debridement and manicuring and, above all, reduction of exposure to irritants (soaps, detergents, alkali, bleaches, solvents, etc). Longitudinal grooving due to temporary lesions of the matrix, such as warts, synovial cysts, and other impingements, may be cured by removal of the offending lesion.

Acute paronychia is treated with topical antibiotics and drainage of the abscess, if present. To incise and drain an acute staphylococcal paronychia, insert a flat metal spatula or sharpened hardwood stick into the nail fold where it adjoins the nail. This will release pus from a mature lesion.

Treatment of chronic paronychia includes minimizing wetwork and toxic contactants, wearing gloves while performing tasks that expose the skin to water, minimizing trauma to the nail folds, and a combination of topical

corticosteroids and an anticandidal twice daily to the affected area.

2. Tinea Unguium (Onychomycosis)

Tinea unguium is a trichophyton infection of one or more (but rarely all) fingernails or toenails. The species most commonly found is *T rubrum*. "Saprophytic" fungi may rarely cause onychomycosis (less than 5% of cases). Evidence supporting a genetic defect in the innate and adaptive immune system may explain why some people suffer from chronic tinea pedis and onychomycosis.

The nails are lusterless, brittle, and hypertrophic, and the substance of the nail is friable. Laboratory diagnosis is mandatory since only 50% of dystrophic nails are due to dermatophytosis. Portions of the nail should be clipped, digested with 10% KOH, and examined under the microscope for hyphae. Fungi may also be cultured from debris collected from underneath the nail plate. Periodic acid-Schiff stain of a histologic section of the nail plate also demonstrates the fungus readily. Each technique is positive in only 50% of cases so several different tests may need to be performed. Periodic acid-Schiff staining of nail plate coupled with fungal culture has a sensitivity of 96%.

Onychomycosis is difficult to treat because of the long duration of therapy required and the frequency of recurrences. Fingernails respond more readily than toenails. For toenails, treatment is indicated for patients with discomfort, inability to exercise, diabetes, and immune compromise.

In general, systemic therapy is required to effectively treat nail onychomycosis. Although historically topical therapy has had limited value, evidence suggests that efinaconazole 10% performs better than other topical treatment options. Tavaborole 5% solution is also approved for the treatment of onychomycosis, but its clearance rates do not appear to be as good as those of efinaconazole. Adjunctive value of surgical procedures is unproven, and the efficacy of laser treatments is lacking, especially with regard to long-term cures.

Fingernails can virtually always be cured, and toenails are cured 35–50% of the time and are clinically improved about 75% of the time. In all cases, before treatment, the diagnosis should be confirmed. The costs of the various treatment options should be known and the most cost-effective treatment chosen. Medication interactions must be avoided. Ketoconazole, due to its higher risk for hepatotoxicity, is not recommended to treat any form of onychomycosis. For fingernails, ultramicronized griseofulvin 250 mg orally three times daily for 6 months can be effective. Alternative treatments are (in order of preference) oral terbinafine, 250 mg daily for 6 weeks; oral itraconazole, 200–400 mg daily for 7 days each month for 2 months; and oral itraconazole, 200 mg daily for 2 months. Off-label use of fluconazole, 150–400 mg once weekly for 6–9 months, can also be effective, but there is limited evidence for this option. Once clear, fingernails usually remain free of disease for some years.

Onychomycosis of the toenails does not respond to griseofulvin therapy. The best treatment, which is also FDA approved, is oral terbinafine 250 mg daily for 12 weeks. Pulse terbinafine therapy with two cycles of 4 weeks on and 4 weeks off may be as efficacious as continuous oral therapy. Liver biochemical tests, CBC, and kidney function should be performed before oral therapy. Because the risk of idiosyncratic injury is very low (transaminitis occurs in less than 0.5% of patients) and the presentation of drug-induced liver injury is usually symptomatic (jaundice, malaise, abdominal pain), routine hepatic monitoring in healthy adults without known hepatic disease is not required. The dose might need adjustment in patients with reduced creatinine clearance. Itraconazole, 200 mg daily for 12 weeks, or pulse oral itraconazole, 200 mg twice daily for 1 week per month for 3 months, is inferior to standard terbinafine treatments, but it is an acceptable alternative for those unable to take terbinafine. The courses of terbinafine or itraconazole may need to be repeated 6 months after the first treatment cycle if fungal cultures of the nail are still positive. Fluconazole may be used off label at 150 mg weekly until the nail has grown out completely (12–18 month for toenails).

Treatment failures are multifactorial but may occur because of mixed infection with non-dermatophyte molds or reinfection. Culture of the nail to determine the organism responsible for infection is critical to choosing the correct therapy. In addition, part of the complete therapeutic regimen for onychomycosis should include replacing or sanitizing potential fungal reservoirs such as socks, shoes, and other textiles. Infected household members should also be treated. Shoes or sandals should be worn in high-risk areas (public showers or pools). Continued prophylactic therapy with topicals such as efinaconazole twice a week to nails and a topical antifungal cream to the feet should be continued for several years or longer after clearance of onychomycosis.

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7 Disorders of the Eyes & Lids

Jacque L. Duncan, MD
Neeti B. Parikh, MD
Gerami D. Seitzman, MD

REFRACTIVE ERRORS

Refractive error is the most common cause of reduced clarity of vision (visual acuity).

Use of a pinhole will overcome most refractive errors and thus allows their identification as a cause of reduced visual acuity. Refractive error can be treated with glasses, contact lenses, or surgery.

Treatment

A. Contact Lenses

An estimated 40.9 million US adults wear contact lenses, mostly for correction of refractive errors, though decorative-colored contact lenses are used.

The major risk from contact lens wear is corneal infection, potentially a blinding condition. Such infections occur more often with soft lenses, particularly extended wear, for which there is at least a fivefold increase in risk of corneal infection compared with daily wear. Decorative contact lenses have a high prevalence of microbial contamination. Contact lens wearers should be made aware of the risks they face and ways to minimize them, such as avoiding overnight wear or use of lenses past their replacement date and maintaining meticulous lens hygiene, including not using tap water or saliva for lens cleaning. Contact lenses should be removed whenever there is ocular discomfort or redness.

Razmaria AA. JAMA patient page. Proper care of contact lenses. JAMA. 2015;314:1534. [PMID: 26462011]

B. Surgery

Various surgical techniques are available to reduce refractive errors, particularly nearsightedness. Laser corneal refractive surgery reshapes the middle layer (stroma) of the cornea with an excimer laser.

Other refractive surgery techniques are extraction of the clear crystalline lens with insertion of a single vision, multifocal, or accommodative intraocular lens as occurs after cataract extraction; insertion of an intraocular lens without removal of the crystalline lens (phakic intraocular lens); intrastromal corneal ring segments (INTACS); collagen cross-linking; laser thermal keratoplasty; and conductive keratoplasty (CK).

Wilkinson JM et al. Refractive eye surgery: helping patients make informed decisions about LASIK. Am Fam Physician. 2017;95:637. [PMID: 28671403]

C. Reduction of Rate of Progression of Nearsightedness

The rate at which nearsightedness progresses can be reduced by topical atropine and pirenzepine, a selective muscarinic antagonist; rigid contact lens wear during sleep (orthokeratology); and various types of soft contact lenses and spectacles, but their long-term efficacy and safety are uncertain.

When to Refer

Any contact lens wearer with an acute painful red eye must be referred emergently for ophthalmologic evaluation.

DISORDERS OF THE LIDS & LACRIMAL APPARATUS

1. Hordeolum

Hordeolum is an acute infection that is commonly due to *Staphylococcus aureus*. It is characterized by a localized red, swollen, acutely tender area on the upper or lower lid. Internal hordeolum is a meibomian gland abscess that usually points onto the conjunctival surface of the lid; external hordeolum, or stye, is usually smaller and on the lid margin and is an abscess of the gland of Zeis.

Warm compresses are helpful. Incision may be indicated if resolution does not begin within 48 hours. An antibiotic ointment (bacitracin or erythromycin) applied to the lid every 3 hours may be beneficial during the acute stage. Internal hordeolum may lead to generalized cellulitis of the lid.

2. Chalazion

Chalazion is a common granulomatous inflammation of a meibomian gland that may follow an internal hordeolum. It is characterized by a hard, nontender swelling on the upper or lower lid with redness and swelling of the adjacent conjunctiva. Initial treatment is with warm compresses. If resolution has not occurred by 2–3 weeks, incision and curettage is indicated. Corticosteroid injection may also be effective.

3. Blepharitis

Blepharitis is a common chronic bilateral inflammatory condition of the lid margins. **Anterior blepharitis** involves the lid skin, eyelashes, and associated glands. It may be ulcerative because of infection by staphylococci, or seborrheic in association with seborrhea of the scalp, brows, and ears. **Posterior blepharitis** results from inflammation of the meibomian glands. There may be bacterial infection, particularly with staphylococci, or primary glandular dysfunction, which is strongly associated with acne rosacea.

Clinical Findings

Symptoms are irritation, burning, and itching. In **anterior blepharitis,** the eyes are "red-rimmed" and scales or collerettes can be seen clinging to the lashes. In **posterior blepharitis,** the lid margins are hyperemic with telangiectasias, and the meibomian glands and their orifices are inflamed. The lid margin is frequently rolled inward to produce a mild entropion, and the tear film may be frothy or abnormally greasy.

Blepharitis is a common cause of recurrent conjunctivitis. Both anterior and, especially, posterior blepharitis may be complicated by hordeola or chalazia; abnormal lid or lash positions, producing trichiasis; epithelial keratitis of the lower third of the cornea; marginal corneal infiltrates; and inferior corneal vascularization and thinning.

Treatment

Anterior blepharitis is usually controlled by eyelid hygiene. Warm compresses help soften the scales and warm the meibomian gland secretions. Eyelid cleansing can be achieved by gentle eyelid massage and lid scrubs with baby shampoo or 0.01% hypochlorous acid. In acute exacerbations, an antibiotic eye ointment, such as bacitracin or erythromycin, is applied daily to the lid margins.

Mild **posterior blepharitis** may be controlled with regular meibomian gland expression and warm compresses. Inflammation of the conjunctiva and cornea is treated with long-term low-dose oral antibiotic therapy, eg, tetracycline (250 mg twice daily for 2–4 weeks), doxycycline (100 mg daily for 2–4 weeks), minocycline (50–100 mg daily for 2–4 weeks) erythromycin (250 mg three times daily for 2–4 weeks), or azithromycin (500 mg daily for 3 days in three cycles with 7-day intervals). Short-term (5–7 days) topical corticosteroids, eg, prednisolone, 0.125% twice daily, may also be indicated. Topical therapy with antibiotics, such as ciprofloxacin 0.3% ophthalmic solution twice daily, may be helpful but should be restricted to short courses of 5–7 days.

Amescua G et al; American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Blepharitis Preferred Practice Pattern®. Ophthalmology. 2019;126:P56. [PMID: 30366800]

4. Entropion & Ectropion

Entropion (inward turning of usually the lower lid) occurs occasionally in older people as a result of degeneration of the lid fascia or may follow extensive scarring of the conjunctiva and tarsus. Surgery is indicated if the lashes rub on the cornea. Botulinum toxin injections may also be used for temporary correction of the involutional lower lid entropion of older people.

Ectropion (outward turning of the lower lid) is common with advanced age. Surgery is indicated if there is excessive tearing, exposure keratitis, or a cosmetic problem.

5. Tumors

Lid tumors are usually benign. Basal cell carcinoma is the most common malignant tumor. Squamous cell carcinoma, meibomian gland carcinoma, and malignant melanoma also occur. Surgery for any lesion involving the lid margin should be performed by an ophthalmologist or suitably trained plastic surgeon to avoid deformity of the lid. Histopathologic examination of eyelid tumors should be routine, since 2% of lesions thought to be benign clinically are found to be malignant. Medications such as vismodegib (an oral inhibitor of the hedgehog pathway), imiquimod (an immunomodulator), and 5-fluorouracil occasionally are used instead of or as an adjunct to surgery for some basal and squamous cell carcinomas.

6. Dacryocystitis

Dacryocystitis is infection of the lacrimal sac usually due to congenital or acquired obstruction of the nasolacrimal system. It may be acute or chronic and occurs most often in infants and in persons over 40 years. It is usually unilateral. Infection is typically with *S aureus* and streptococci in acute dacryocystitis and *Staphylococcus epidermidis*, streptococci, or gram-negative bacilli in chronic dacryocystitis.

Acute dacryocystitis is characterized by pain, swelling, tenderness, and redness in the tear sac area; purulent material may be expressed. In chronic dacryocystitis, tearing and discharge are the principal signs, and mucus or pus may also be expressed.

Acute dacryocystitis responds well to systemic antibiotic therapy. To relieve the underlying obstruction, surgery is usually done electively but may be performed urgently in acute cases. The chronic form may be kept latent with systemic antibiotics, but relief of the obstruction is the only cure. In adults, the standard procedure is dacryocystorhinostomy, which involves surgical exploration of the lacrimal sac and formation of a fistula into the

nasal cavity and, if necessary, supplemented by nasolacrimal intubation.

Congenital nasolacrimal duct obstruction is common and often resolves spontaneously. It can be treated by probing the nasolacrimal system, supplemented by nasolacrimal intubation or balloon catheter dilation, if necessary; dacryocystorhinostomy is rarely required.

CONJUNCTIVITIS

Conjunctivitis is inflammation of the mucous membrane that lines the surface of the eyeball and inner eyelids. It may be acute or chronic. Most cases are due to viral or bacterial (including gonococcal and chlamydial) infection. Other causes include keratoconjunctivitis sicca, allergy, chemical irritants, and trauma. The mode of transmission of infectious conjunctivitis is usually via direct contact of contaminated fingers or objects to the other eye or to other persons. It may also be spread through respiratory secretions or contaminated eye drops.

Conjunctivitis must be differentiated from acute uveitis, acute glaucoma, and corneal disorders (Table 7–1).

Varu DM et al; American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Conjunctivitis Preferred Practice Pattern®. Ophthalmology. 2019;126:P94. [PMID: 30366797]

1. Viral Conjunctivitis

Adenovirus is the most common cause of viral conjunctivitis. There is usually sequential bilateral disease with copious watery discharge and a follicular conjunctivitis. Infection spreads easily. Epidemic keratoconjunctivitis, which may result in decreased vision from corneal subepithelial infiltrates, is usually caused by adenovirus types 8, 19, and 37. The active viral conjunctivitis lasts up to 2 weeks, with the immune-mediated keratitis occurring later. Infection with adenovirus types 3, 4, 7, and 11 is typically associated with pharyngitis, fever, malaise, and preauricular adenopathy (pharyngoconjunctival fever). The disease usually lasts 10 days. Contagious acute hemorrhagic conjunctivitis (see Chapter 32) may be caused by enterovirus 70 or coxsackievirus A24, though etiologies vary globally. Viral conjunctivitis from herpes simplex virus (HSV) is typically unilateral and may be associated with lid vesicles.

Except for HSV infection for which treatment with topical (eg, ganciclovir 0.15% gel) and/or systemic (eg, oral acyclovir, valacyclovir) antivirals is recommended (Table 32–1), there is no specific treatment for contagious viral conjunctivitis. Artificial tears and cold compresses may help reduce discomfort. The use of topical antibiotics and steroids in the acute infection is discouraged. Frequent hand and linen hygiene is encouraged to minimize spread.

Kaur G, Seitzman GD et al. Keeping an eye on pink eye: a global conjunctivitis outbreak expert survey. Int Health. 2021 Aug 19. [Epub ahead of print] [PMID: 34409991]

2. Bacterial Conjunctivitis

The organisms isolated most commonly in bacterial conjunctivitis are staphylococci, including methicillin-resistant *S aureus* (MRSA); streptococci, particularly *Streptococcus pneumoniae*; *Haemophilus* species; *Pseudomonas;* and *Moraxella*. All may produce purulent discharge and eyelid matting. Blurring of vision and discomfort are mild. In severe (hyperpurulent) cases, examination of stained conjunctival scrapings and cultures is recommended, particularly to identify gonococcal infection that requires emergent treatment.

The disease is usually self-limited, lasting about 10–14 days if untreated. Most topical antibiotics hasten clinical remission.

Table 7–1. The inflamed eye: differential diagnosis of common causes.

	Acute Conjunctivitis	Acute Anterior Uveitis (Iritis)	Acute Angle-Closure Glaucoma	Corneal Trauma or Infection
Incidence	Extremely common	Common	Uncommon	Common
Discharge	Moderate to copious	None	None	Watery or purulent
Vision	No effect on vision	Often blurred	Markedly blurred	Usually blurred
Pain	Mild	Moderate	Severe	Moderate to severe
Conjunctival injection	Diffuse	Mainly circumcorneal	Mainly circumcorneal	Mainly circumcorneal
Cornea	Clear	Usually clear	Cloudy	Clarity change related to cause
Pupil size	Normal	Small	Moderately dilated	Normal or small
Pupillary light response	Normal	Poor	None	Normal
Intraocular pressure	Normal	Usually normal but may be elevated	Markedly elevated	Normal
Smear	Causative organisms	No organisms	No organisms	Organisms found only in corneal infection

This infection is typically self-limited, and no topical antibiotic has proven superiority over another.

A. Gonococcal Conjunctivitis

Gonococcal conjunctivitis, usually acquired through contact with infected genital secretions, typically causes copious purulent discharge. It is an ophthalmologic emergency because corneal involvement may rapidly lead to perforation. The diagnosis should be confirmed by stained smear and culture of the discharge. Systemic treatment is required with a single 500-mg dose of intramuscular ceftriaxone if the patient weighs less than 150 kg or 1-g dose if patient weighs more than 150 kg (see Chapter 33). Fluoroquinolone resistance is common. Eye irrigation with saline may promote resolution of conjunctivitis. Topical antibiotics such as erythromycin and bacitracin may be added. Other sexually transmitted diseases, including chlamydiosis, syphilis, and HIV infection, should be considered. Routine treatment for chlamydial infection is recommended.

Alsoudi AF… Seitzman GD. Purulent conjunctivitis and progressive corneal stromal necrosis. JAMA Ophthalmol. 2021;139:908. [PMID: 34081098]

B. Chlamydial Keratoconjunctivitis

1. Trachoma—Trachoma is the most common infectious cause of blindness worldwide, with approximately 40 million people affected and 1.2 million blind. Recurrent episodes of infection in childhood manifest as bilateral follicular conjunctivitis, epithelial keratitis, and corneal vascularization (pannus). Scarring (cicatrization) of the tarsal conjunctiva leads to entropion and trichiasis in adulthood with secondary central corneal scarring.

Immunologic tests or PCR on conjunctival samples will confirm the diagnosis but treatment should be started on the basis of clinical findings. A single 1-g dose of oral azithromycin is the preferred drug for mass treatment campaigns; improvements in hygiene and living conditions probably have contributed more to the marked reduction in the prevalence of trachoma during the past 30 years. Local treatment is not necessary. Surgical treatment includes correction of lid deformities and corneal transplantation.

Godwin W et al. Trachoma prevalence after discontinuation of mass azithromycin distribution. J Infect Dis. 2020;221:S519. [PMID: 32052842]

2. Inclusion conjunctivitis—The eye becomes infected after contact with genital secretions infected with chlamydia. The disease starts with acute redness, discharge, and irritation. Examination shows follicular conjunctivitis with mild keratitis. A nontender preauricular lymph node can often be palpated. Healing usually leaves no sequelae. Diagnosis can be rapidly confirmed by immunologic tests or PCR on conjunctival samples. Treatment is doxycycline, 100 mg orally twice a day for 7 days. All cases should be assessed for genital tract infection and other sexually transmitted diseases.

3. Dry Eyes

Dry eye, a common and chronic disorder, is an umbrella term that describes a condition of tear film instability and associated ocular and visual complaints. Dry eye is more common in women than men and increases with age. Hypofunction of the lacrimal glands, causing loss of the aqueous component of tears (keratoconjunctivitis sicca), may be due to aging, hereditary disorders, systemic disease (eg, Sjögren syndrome), or systemic drugs. Excessive evaporation of tears may be due to environmental factors (eg, excessive screen time, windy climate) or abnormalities of the lipid component of the tear film, as in blepharitis. Mucin deficiency may be due to vitamin A deficiency or conjunctival scarring from trachoma, Stevens-Johnson syndrome, mucous membrane pemphigoid, graft-versus-host disease, chemical burns, or topical drug toxicity.

Clinical Findings

The patient complains of dryness, redness, foreign body sensation, and variable vision. In severe cases, there is persistent marked discomfort, with photophobia, difficulty in moving the lids, and excessive mucus secretion. In many cases, gross inspection reveals no abnormality, but on slit-lamp examination there are abnormalities of tear film stability and reduced tear volume. In more severe cases, damaged corneal and conjunctival cells stain with fluorescein and lissamine green. In the most severe cases, there is marked conjunctival injection, mucoid discharge, loss of the normal conjunctival and corneal luster, and epithelial keratopathy that stains with fluorescein and may progress to frank ulceration. The Schirmer test, which measures the rate of production of the aqueous component of tears, may be helpful.

Treatment

Aqueous deficiency can be treated with artificial tears drops or ointments. The simplest preparations are physiologic (0.9%) or hypo-osmotic (0.45%) solutions of sodium chloride, which can be used as frequently as every half-hour, but in most cases are needed only three or four times a day. More prolonged duration of action can be achieved with drop preparations containing a mucomimetic such as hydroxypropyl methylcellulose (HPMC) or carboxymethylcelluose (carmellose).

Artificial tear preparations are generally safe and, in most cases, are used three or four times a day. However, preservatives included in some preparations to maintain sterility are potentially toxic and allergenic and may cause ocular surface toxicity in frequent users. Such reactions may be misinterpreted as a worsening of the dry eye state requiring more frequent use of the artificial tears and leading in turn to further deterioration, rather than being recognized as a need to change to a preservative-free preparation. Preservative-free preparations are recommended for any frequency of use greater than four times a day. Eye drops claiming to "get the red out" are not

recommended as they cause toxicity and rebound hyperemia with prolonged use.

Dry eye is considered an inflammatory ocular surface disease. Accordingly, disease modification may require episodic treatment with low potency corticosteroid drops. All patients using topical corticosteroids should have their intraocular pressure monitored by eye care professionals. Corticosteroid-sparing anti-inflammatory drops such as the calcineurin inhibitor cyclosporine 0.05% ophthalmic emulsion (Restasis) and the integrin antagonist lifitegrast 5% are commonly used with no universal consensus of efficacy. Lacrimal punctal occlusion by canalicular plugs or cautery is useful in severe cases.

Blepharitis is treated as described above.

de Paiva CS et al. Topical cyclosporine A therapy for dry eye syndrome. Cochrane Database Syst Rev. 2019;9:CD010051. [PMID: 31517988]

Gonzales JA… Seitzman GD et al. Ocular clinical signs and diagnostic tests most compatible with keratoconjunctivitis sicca: a latent class approach. Cornea. 2020;39:1013. [PMID: 32251167]

4. Allergic Eye Disease

Allergic eye disease is common and takes a number of different forms, but all are expressions of atopy, which may also manifest as atopic asthma, atopic dermatitis, or allergic rhinitis.

Clinical Findings

Symptoms include itching, tearing, redness, stringy discharge, and occasionally, photophobia and visual loss.

Allergic conjunctivitis is common. It may be seasonal (hay fever), developing usually during the spring or summer, or perennial. Clinical signs include conjunctival hyperemia and edema (chemosis), the latter at times being marked and sudden in onset. **Vernal keratoconjunctivitis** also tends to occur in late childhood and early adulthood. It is usually seasonal, with a predilection for the spring. Large "cobblestone" papillae are noted on the upper tarsal conjunctiva. There may be follicles at the limbus. **Atopic keratoconjunctivitis** is a more chronic disorder of adulthood. Both the upper and the lower tarsal conjunctivas exhibit a papillary conjunctivitis. Severe cases demonstrate conjunctival fibrosis, resulting in forniceal shortening and entropion with trichiasis. Corneal involvement, including refractory ulceration, is frequent during exacerbations of both vernal and severe atopic keratoconjunctivitis. The latter may be complicated by herpes simplex keratitis.

Treatment

A. Mild and Moderately Severe Allergic Eye Disease

Topical anti-inflammatory agents include mast cell stabilizers and antihistamines (Table 7–2). Mast cell stabilization takes longer to act than antihistamines but can be useful for prophylaxis. Topical vasoconstrictors, such as ephedrine, naphazoline, tetrahydrozoline, and phenylephrine, alone or in combination with antihistamines, are available as over-the-counter medications and not typically used because of limited efficacy, rebound hyperemia, and follicular conjunctivitis. Systemic antihistamines (eg, loratadine 10 mg orally daily) may be useful in prolonged atopic keratoconjunctivitis. In allergic conjunctivitis, specific allergens may be avoidable.

B. Acute Exacerbations and Severe Allergic Eye Disease

Topical corticosteroids (Table 7–2) are essential to control acute exacerbations of both vernal and atopic keratoconjunctivitis. Corticosteroid-induced side effects should be monitored by eye care professionals and include cataracts, glaucoma, and exacerbation of herpes simplex keratitis. The lowest potency corticosteroid that controls ocular inflammation should be used. Topical cyclosporine or tacrolimus is also effective. Systemic corticosteroid or other immunosuppressant therapy may be required in severe atopic keratoconjunctivitis.

Beck KM, Seitzman GD et al. Ocular co-morbidities of atopic dermatitis. Part I: associated ocular diseases. Am J Clin Dermatol. 2019;20:797. [PMID: 31359350]

Beck KM, Seitzman GD et al. Ocular co-morbidities of atopic dermatitis. Part II: ocular disease secondary to treatments. Am J Clin Dermatol. 2019;20:807. [PMID: 31352589]

PINGUECULA & PTERYGIUM

Pinguecula is a yellowish, elevated conjunctival nodule in the area of the palpebral fissure. It is common in persons over age 35 years. Pterygium is a fleshy, triangular encroachment of the conjunctiva onto the cornea and is usually associated with prolonged exposure to wind, sun, sand, and dust. Pinguecula and pterygium are often bilateral and occur more frequently on the nasal side of the conjunctiva.

Pingueculae rarely grow but may become inflamed (pingueculitis). Pterygia become inflamed and may grow. Treatment is rarely required for inflammation of pinguecula or pterygium, and artificial tears are often beneficial.

The indications for excision of pterygium are growth that threatens vision by encroaching on the visual axis, marked induced astigmatism, or severe ocular irritation.

Shahraki T et al. Pterygium: an update on pathophysiology, clinical features, and management. Ther Adv Ophthalmol. 2021;13:25158414211020152. [PMID: 34104871]

CORNEAL ULCER

Corneal ulcers are most commonly due to infection by bacteria, viruses, fungi, or amoebas. Noninfectious causes—all of which may be complicated by infection—include neurotrophic keratitis (resulting from loss of

Table 7–2. Topical ophthalmic agents (selected list).

Agent	Cost/Size[1]	Recommended Regimen	Indications
Antibiotic Agents			
Amikacin 2.5% (fortified) solution	Compounding pharmacy		
Azithromycin (AzaSite)	$267.25/2.5 mL	1 drop two times daily for 2 days, then once daily for 5 days	Bacterial conjunctivitis
Bacitracin 500 U/g ointment (various)[2]	$118.44/3.5 g	Apply 0.5 inch into lower conjunctival sac or to eyelids three to four times daily for 7–10 days	Bacterial conjunctivitis, blepharitis, sty
Bacitracin/Polymyxin ointment (Polysporin, AK-Poly)	$25.70/3.5 g	Apply 0.5 inch into lower conjunctival sac and then three to four times daily, then as required	Corneal abrasion Following corneal foreign body removal
Besifloxacin ophthalmic suspension, 0.6% (Besivance)	$242.05/5 mL	1–2 drops every 2 hours while awake for 2 days, then every 4 hours for 5 days 1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce	Bacterial conjunctivitis Bacterial keratitis
Ciprofloxacin HCl 0.3% solution (Ciloxan)	$11.09/5 mL	1–2 drops every 2 hours while awake for 2 days, then every 4 hours for 5 days 1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce	Bacterial conjunctivitis Bacterial keratitis
Ciprofloxacin HCl 0.3% ointment	$257.23/3.5 g	Apply 0.5 inch into lower conjunctival sac three times daily for 2 days, then two times daily for 5 days	Bacterial conjunctivitis
Erythromycin 0.5% ointment (various)	$17.96/3.5 g	1-cm ribbon up to six times daily	Bacterial infection of the conjunctiva or lid margin
Fusidic acid 1% gel (Fucithalmic)	Not available in United States	1 drop two times daily	Bacterial conjunctivitis, blepharitis, sty, keratitis
Gatifloxacin 0.5% solution (Zymaxid)	$118.16/2.5 mL	1 drop every 2 hours while awake, up to eight times on day 1, then two to four times daily while awake, days 2–7 1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce	Bacterial conjunctivitis Bacterial keratitis
Gentamicin sulfate 0.3% solution (various)	$19.18/5 mL	1–2 drops every 4 hours up to 2 drops every hour for severe infections	Ocular surface infection
Gentamicin sulfate 0.3% ointment (various)	$38.95/3.5 g	Apply 0.5 inch into lower conjunctival sac two to three times daily	Ocular surface infection
Gentamicin sulfate 1.5% (fortified preparation)	Compounding pharmacy	1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce	Bacterial keratitis

(*continued*)

Table 7–2. Topical ophthalmic agents (selected list). (continued)

Agent	Cost/Size[1]	Recommended Regimen	Indications
Levofloxacin 0.5% solution (various)	$75.00/5 mL	1–2 drops every 2 hours while awake for 2 days (maximum eight times per day), then every 4 hours for 5 days (maximum four times per day) 1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce	Bacterial conjunctivitis Bacterial keratitis
Moxifloxacin 0.5% solution (Vigamox)	$13.92/3 mL	1 drop three times daily for 7 days 1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce	Bacterial conjunctivitis Bacterial keratitis
Neomycin/Polymyxin B/Gramicidin (Neosporin)	$61.26/10 mL	1–2 drops every 4 hours for 7–10 days or more frequently, as required	Ocular surface infection
Norfloxacin 0.3% solution	Not available in United States	1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce	Ocular surface infection Bacterial keratitis
Ofloxacin 0.3% solution (Ocuflox)	$20.94/5 mL	1–2 drops every 2–4 hours for 2 days, then four times daily for 5 days 1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce	Bacterial conjunctivitis Bacterial keratitis
Polymyxin B 10,000 U/mL/ Trimethoprim sulfate 1 mg/mL (Polytrim)[3]	$12.87/10 mL	1 drop every 3 hours for 7–10 days (maximum of 6 doses per day)	Ocular surface infection
Propamidine isethionate 0.1% solution	Not available in the United States	1–2 drops every 2–4 hours for 2 days, then four times daily for 5 days	Ocular surface infection (including *Acanthamoeba* keratitis)
Propamidine isethionate 0.1% ointment	Not available in the United States	Apply 0.5 inch into lower conjunctival sac up to four times daily	
Sulfacetamide sodium 10% solution (various)	$55.65/15 mL	1 or 2 drops every 2–3 hours initially; taper by increasing time intervals as condition responds; usual duration 7–10 days	Bacterial infection of the conjunctiva or lid margin
Sulfacetamide sodium 10% ointment (various)	$65.86/3.5 g	Apply 0.5 inch into lower conjunctival sac once every 3–4 hours and at bedtime; taper by increasing time intervals as condition responds; usual duration 7–10 days	Bacterial infection of the conjunctiva or lid margin
Tobramycin 0.3% solution (various)	$6.25/5 mL	1–2 drops every 4 hours for a mild to moderate infection or hourly until improvement (then reduce prior to discontinuation) for a severe infection	
Tobramycin 1.5% (fortified) solution	Compounding pharmacy	1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce	Bacterial keratitis

(*continued*)

Table 7–2. Topical ophthalmic agents (selected list). (continued)

Agent	Cost/Size[1]	Recommended Regimen	Indications
Tobramycin 0.3% ointment (Tobrex)	$257.23/3.5 g	Apply 0.5 inch into lower conjunctival sac two to three times daily for a mild to moderate infection or every 3–4 hours until improvement (then reduce prior to discontinuation) for a severe infection	
Antifungal Agents			
Amphotericin 0.1–0.5% solution	Compounding pharmacy		Fungal blepharitis, conjunctivitis, keratitis
Natamycin 5% suspension (Natacyn)	$568.37/15 mL	1 drop every 1–2 hours initially	
Voriconazole 1% solution	Compounding pharmacy		
Antiviral Agents			
Acyclovir 3% ointment (Zovirax)	Not available in United States	Five times daily	Herpes simplex keratitis
Ganciclovir 0.15% gel (Zirgan)	$502.03/5 g	Five times daily	
Trifluridine 1% solution (Viroptic)	$178.28/7.5 mL	1 drop onto cornea every 2 hours while awake for a maximum daily dose of 9 drops until resolution occurs; then an additional 7 days of 1 drop every 4 hours while awake (minimum five times daily)	
Anti-Inflammatory Agents			
Antihistamines[4]			
Emedastine difumarate 0.05% solution (Emadine)	Not available in the United States	1 drop four times daily	Allergic eye disease
Levocabastine (Livostin)	Not available in United States	1 drop twice daily	
Mast cell stabilizers			
Cromolyn sodium 4% solution (Crolom)	$37.20/10 mL	1 drop four to six times daily	
Lodoxamide tromethamine 0.1% solution (Alomide)	$205.28/10 mL	1 or 2 drops four times daily (up to 3 months)	
Nedocromil sodium 2% solution (Alocril)	$269.41/5 mL	1 drop twice daily	
Pemirolast potassium 0.1% solution (Alamast)	Not available in the United States	1 drop four times daily	
Combined antihistamines and mast cell stabilizers			
Alcaftadine 0.25% ophthalmic solution (Lastacaft)	$283.99/3 mL	1 drop once daily	
Azelastine HCl 0.05% ophthalmic solution (Optivar)	$102.90/6 mL	1 drop two to four times daily (up to 6 weeks)	
Bepotastine besilate 1.5% solution (Bepreve)	$498.51/10 mL	1 drop twice daily	
Epinastine hydrochloride 0.05% ophthalmic solution (Elestat)	$106.95/5 mL	1 drop twice daily (up to 8 weeks)	
Ketotifen fumarate 0.025% solution (Zaditor)	OTC $7.79/5 mL	1 drop two to four times daily	
Olopatadine hydrochloride 0.1% solution (Patanol)	OTC $12.42/5 mL	1 drop twice daily	

(*continued*)

Table 7–2. Topical ophthalmic agents (selected list). (continued)

Agent	Cost/Size[1]	Recommended Regimen	Indications
Nonsteroidal anti-inflammatory agents			
Bromfenac 0.09% solution (Xibrom)	$213.69/1.7 mL	1 drop to operated eye twice daily beginning 24 hours after cataract surgery and continuing through 2 postoperative weeks	Treatment of postoperative inflammation following cataract extraction
Diclofenac sodium 0.1% solution (Voltaren)	$17.50/5 mL	1 drop to operated eye four times daily beginning 24 hours after surgery and continuing through 2 postoperative weeks	Treatment of postoperative inflammation following cataract extraction and laser corneal surgery
Flurbiprofen sodium 0.03% solution (various)	$51.50/2.5 mL	1 drop every half hour beginning 2 hours before surgery; 1 drop to operated eye four times daily beginning 24 hours after cataract surgery	Inhibition of intraoperative miosis; treatment of cystoid macular edema and inflammation after cataract extraction
Indomethacin 1% solution (Indocid)	Not available in United States	1 drop four times daily	Treatment of allergic eye disease, postoperative inflammation following cataract extraction and laser corneal surgery
Ketorolac tromethamine 0.5% solution (Acular)	$105.50/5 mL	1 drop four times daily	
Nepafenac 0.1% suspension (Nevanac)	$325.96/3 mL	1 drop to operated eye three times daily beginning 24 hours after cataract surgery and continuing through 2 postoperative weeks	Treatment of postoperative inflammation following cataract extraction
Corticosteroids[5]			
Dexamethasone sodium phosphate 0.1% solution (various)	$21.10/5 mL	1 or 2 drops as often as indicated by severity; use every hour during the day and every 2 hours during the night in severe inflammation; taper off as inflammation decreases	Treatment of steroid-responsive inflammatory conditions
Dexamethasone sodium phosphate 0.05% ointment	Compounding pharmacy	Apply thin coating on lower conjunctival sac three or four times daily	
Fluorometholone 0.1% suspension (various)[6]	$202.10/5 mL	1 or 2 drops as often as indicated by severity; use every hour during the day and every 2 hours during the night in severe inflammation; taper off as inflammation decreases	
Fluorometholone 0.25% suspension (FML Forte)[6]	$404.22/10 mL	1 drop two to four times daily	
Fluorometholone 0.1% ointment (FML S.O.P.)	$192.48/3.5 g	Apply thin coating on lower conjunctival sac three or four times daily	
Loteprednol etabonate 0.5% (Lotemax)	$450.67/10 mL	1 or 2 drops four times daily	
Prednisolone acetate 0.12% suspension (Pred Mild)	$384.97/10 mL	1 or 2 drops as often as indicated by severity of inflammation; use every hour during the day and every 2 hours during the night in severe inflammation; taper off as inflammation decreases	
Prednisolone sodium phosphate 0.125% solution	Compounding pharmacy		
Prednisolone acetate 1% suspension (various)	$105.60/10 mL	2 drops four times daily	
Prednisolone sodium phosphate 1% solution (various)	$63.25/10 mL	1–2 drops two to four times daily	

(*continued*)

Table 7–2. Topical ophthalmic agents (selected list). (continued)

Agent	Cost/Size[1]	Recommended Regimen	Indications
Immunomodulators			
Cyclosporine 0.05% emulsion (Restasis) 0.4 mL/container	$367.99/30 containers	1 drop twice daily	Dry eyes and severe allergic eye disease
Tacrolimus 0.1% ointment	$84.00/30 g tube	Apply to lower conjunctival sac twice daily	Severe allergic eye disease
Glaucoma and Ocular Hypertension Agents			
Sympathomimetics			
Apraclonidine HCl 0.5% solution (Iopidine)	$86.77/5 mL	1 drop three times daily	Reduction of intraocular pressure; expensive; reserve for treatment of resistant cases
Apraclonidine HCl 1% solution (Iopidine)	$33.27/unit dose	1 drop 1 hour before and immediately after anterior segment laser surgery	To control or prevent elevations of intraocular pressure after laser trabeculoplasty or iridotomy
Brimonidine tartrate 0.2% solution (Alphagan, Alphagan P [benzalkonium chloride-free])	$12.50/5 mL	1 drop two or three times daily	Reduction of intraocular pressure
Beta-adrenergic blocking agents			
Betaxolol HCl 0.5% solution (Betoptic) and 0.25% suspension (Betoptic S)[7]	0.5%: $117.91/10 mL 0.25%: $372.64/10 mL	1 drop twice daily	Reduction of intraocular pressure
Carteolol HCl 1% and 2% solution (various, Teoptic)[8]	1%: $40.10/10 mL	1 drop twice daily	
Levobunolol HCl 0.25% and 0.5% solution (Betagan)[9]	0.5%: $21.49/5 mL	1 drop once or twice daily	
Metipranolol HCl 0.3% solution (OptiPranolol)[9]	$29.67/5 mL	1 drop twice daily	
Timolol 0.25% and 0.5% solution (Betimol)[9]	0.5%: $182.83/5 mL	1 drop once or twice daily	
Timolol maleate 0.25% and 0.5% solution (Istalol, Ocudose [preservative-free], Timoptic) and 0.1%, 0.25%, and 0.5% gel (Timoptic-XE, Timoptic GFS)[9]	0.5% solution: $6.56/5 mL 0.5% gel: $217.27/5 mL	1 drop once or twice daily	
Miotics			
Pilocarpine HCl 1–4% solution[10]	1% solution: $92.73/15 mL	1 drop up to four times daily for elevated intraocular pressure	Reduction of intraocular pressure, treatment of acute or chronic angle-closure glaucoma, and pupillary constriction
Carbonic anhydrase inhibitors			
Brinzolamide 1% suspension (Azopt)	$366.01/10 mL	1 drop three times daily	Reduction of intraocular pressure
Dorzolamide HCl 2% solution (Trusopt)	$40.79/10 mL	1 drop three times daily	

(*continued*)

Table 7–2. Topical ophthalmic agents (selected list). (continued)

Agent	Cost/Size[1]	Recommended Regimen	Indications
Prostaglandin analogs			
Bimatoprost 0.03% solution (Lumigan)	$138.87/3 mL	1 drop once daily at night	Reduction of intraocular pressure
Latanoprost 0.005% solution (Xalatan, Monopost [preservative-free])	$27.26/2.5 mL (Monopost not available in United States)	1 drop once or twice daily at night	
Latanoprostene bunod 0.024% solution (Vyzulta)	$272.70/2.5 mL	1 drop daily at night	
Tafluprost 0.0015% solution (Saflutan [preservative-free], Taflotan, Zioptan [preservative-free])	$276.06/30 units (Saflutan not available in United States)	1 drop once daily at night	
Travoprost 0.004% solution (Travatan, Travatan Z [benzalkonium chloride-free])	$198.36/2.5 mL	1 drop once daily at night	
Unoprostone isopropyl 0.15% solution (Rescula)	$153.84/5 mL	1 drop twice daily	
Rho kinase inhibitor			
Netarsudil ophthalmic solution 0.02% (Rhopressa)	$356.52/2.5 mL	1 drop daily in the evening	Reduction of intraocular pressure
Combined preparations			
Bimatoprost 0.03% and timolol 0.5% (Ganfort)	Not available in United States	1 drop daily in the morning	Reduction of intraocular pressure
Brimonidine 0.2% and timolol 0.5% (Combigan)	$443.27/10 mL	1 drop twice daily	
Brimonidine 0.2% and brinzolamide 1% (Simbrinza)	$228.86/8 mL	1 drop three times a day	
Brinzolamide 1% and timolol 0.5% (Azarga)	Not available in United States	1 drop twice daily	
Dorzolamide 2% and timolol 0.5% (Cosopt, Cosopt PF [preservative-free])	$169.51/10 mL	1 drop twice daily	
Latanoprost 0.005% and timolol 0.5% (Xalacom)	Not available in United States	1 drop daily in the morning	
Tafluprost 0.0015% and timolol 0.5% (Taptiqom [preservative-free])	Not available in United States	1 drop daily	
Travoprost 0.004% and timolol 0.5% (DuoTrav)	Not available in United States	1 drop daily	

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. IBM Micromedex Red Book (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www-micromedexsolutions-com.proxy.hsl.ucdenver.edu/(cited March 15, 2022). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.
[2]Little efficacy against gram-negative organisms (except *Neisseria*).
[3]No gram-positive coverage.
[4]May produce rebound hyperemia and local reactions.
[5]Long-term use increases intraocular pressure, causes cataracts, and predisposes to bacterial, herpes simplex virus, and fungal keratitis. These problems may be attenuated by the ester corticosteroid loteprednol.
[6]Less likely to elevate intraocular pressure.
[7]Cardioselective (beta-1) beta-blocker.
[8]Teoptic is not available in the United States.
[9]Nonselective (beta-1 and beta-2) beta-blocker. Monitor all patients for systemic side effects, particularly exacerbation of asthma.
[10]Decreased night vision and headaches possible.

corneal sensation), exposure keratitis (due to inadequate lid closure), severe dry eye, severe allergic eye disease, and inflammatory disorders that may be purely ocular or part of a systemic vasculitis. Delayed or ineffective treatment of corneal ulceration may lead to devastating consequences with corneal scarring and rarely intraocular infection. Prompt referral is essential.

Patients complain of pain, photophobia, tearing, and reduced vision. The conjunctiva is injected, and there may be purulent or watery discharge. The corneal appearance varies according to the underlying cause.

When to Refer

Any patient with an acute painful red eye and corneal abnormality should be referred emergently to an ophthalmologist. Contact lens wearers with acute eye pain, redness, and decreased vision should be referred immediately.

INFECTIOUS KERATITIS

1. Bacterial Keratitis

Risk factors for bacterial keratitis include contact lens wear—especially overnight wear—and corneal trauma, including refractive surgery. The pathogens most commonly isolated are staphylococci, including MRSA; streptococci; and *Pseudomonas aeruginosa, Moraxella* species, and other gram-negative bacilli. The cornea has an epithelial defect and an underlying opacity. Hypopyon may be present. Topical fluoroquinolones, such as levofloxacin 0.5%, ofloxacin 0.3%, norfloxacin 0.3%, or ciprofloxacin 0.3%, are commonly used as first-line agents as long as local prevalence of resistant organisms is low (Table 7–2). For severe central ulcers, diagnostic scrapings can be sent for Gram stain and culture. Treatment may include compounded high-concentration topical antibiotic drops applied hourly day and night for at least the first 48 hours. Fourth-generation fluoroquinolones (moxifloxacin 0.5% and gatifloxacin 0.3%) are also frequently used in this setting. Although early adjunctive topical corticosteroid therapy may improve visual outcome, it should be prescribed only by an ophthalmologist.

When to Refer

Any patient with suspected bacterial keratitis must be referred emergently to an ophthalmologist.

Lin A et al; American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Bacterial keratitis: Preferred Practice Pattern®. Ophthalmology. 2019; 126:P1. [PMID: 30366799]

2. Herpes Simplex Keratitis

Primary ocular herpes simplex virus infection may manifest as lid, conjunctival, or corneal ulceration. The ability of the virus to colonize the trigeminal ganglion leads to recurrences that may be precipitated by fever, excessive exposure to sunlight, or immunodeficiency. Herpetic corneal disease is typically unilateral but can be seen bilaterally in the setting of atopy or immunocompromise. The dendritic (branching) corneal ulcer is the most characteristic manifestation of herpetic corneal disease. More extensive ("geographic") ulcers also occur, particularly if topical corticosteroids have been used. The corneal ulcers are most easily seen after instillation of fluorescein and examination with a cobalt blue light. Resolution of corneal herpetic disease is hastened by treatment with topical antiviral agents (eg, trifluridine drops, ganciclovir gel, acyclovir ointment) or oral antiviral agents (eg, acyclovir, 400–800 mg five times daily or valacyclovir 500–1000 mg three times daily for 7–14 days). Topical antiviral agents may cause corneal toxicity after approximately 10–14 days of therapy and for that reason are not commonly used for long-term suppressive therapy.

Stromal herpes simplex keratitis produces increasingly severe corneal opacity with each recurrence. Antiviral agents alone are insufficient to control stromal disease, so topical corticosteroids are also used, but they may enhance viral replication and steroid dependence frequently occurs. **Caution:** *For patients with known or possible herpetic disease, topical corticosteroids should be prescribed only with ophthalmologic supervision.* Severe stromal scarring may require corneal transplantation; recurrence in the new cornea is common and long-term oral antiviral agents are required.

The rate of recurrent corneal herpetic disease is reduced by using long-term oral acyclovir, 400 mg twice daily; famciclovir, 250 mg once daily; or valacyclovir, 500 mg once daily. Long-term oral antiviral dosing may be adjusted if the disease breaks through suppressive dosing or if kidney dysfunction is present.

When to Refer

Any patient with a history of herpes simplex keratitis and an acute red eye should be referred urgently to an ophthalmologist.

Azher TN et al. Herpes simplex keratitis: challenges in diagnosis and clinical management. Clin Ophthalmol. 2017;11:185. [PMID: 28176902]

Poon SHL et al. A systematic review on advances in diagnostics for herpes simplex keratitis. Surv Ophthalmol. 2021;66:514. [PMID: 33186564]

3. Herpes Zoster Ophthalmicus

Herpes zoster frequently involves the ophthalmic division of the trigeminal nerve. It presents with malaise, fever, headache, and periorbital burning and itching. These symptoms may precede the eruption by a day or more. The rash is initially vesicular, quickly becoming pustular and then crusting. Involvement of the tip of the nose or the lid margin predicts involvement of the eye. Ocular signs include conjunctivitis, keratitis, episcleritis, and anterior uveitis, often with elevated intraocular pressure.

Recurrent anterior segment inflammation, neurotrophic keratitis, and posterior subcapsular cataract are long-term complications. Optic neuropathy, cranial nerve palsies, acute retinal necrosis, and cerebral angiitis occur infrequently. HIV infection is an important risk factor for herpes zoster ophthalmicus and increases the likelihood of complications.

High-dose oral acyclovir (800 mg five times a day), valacyclovir (1 g three times a day), or famciclovir (500 mg three times a day) for 7–10 days started within 72 hours after the appearance of the rash reduces the incidence of ocular complications but not of postherpetic neuralgia. Acute keratitis, or a "pseudo-dendrite," can be treated with a topical antiviral such as ganciclovir 0.15% gel, 1 drop five times daily until healing has occurred and then 1 drop three times daily for 1 more week. Anterior uveitis requires additional treatment with topical corticosteroids and cycloplegics. Topical corticosteroids, which promote viral replication, may have to be delayed until the keratitis has resolved. Neurotrophic keratitis is an important cause of long-term morbidity.

When to Refer

Any patient with herpes zoster ophthalmicus and ocular symptoms or signs should be referred urgently to an ophthalmologist.

Davis AR et al. Herpes zoster ophthalmicus review and prevention. Eye Contact Lens. 2019;45:286. [PMID: 30844951]
Vrcek I et al. Herpes zoster ophthalmicus: a review for the internist. Am J Med. 2017;130:21 [PMID: 27644149]

4. Fungal Keratitis

Fungal keratitis tends to occur after corneal injury involving plant material or in an agricultural setting, in eyes with chronic ocular surface disease, and in contact lens wearers. It may be an indolent process. The corneal infiltrate may have feathery edges and multiple "satellite" lesions. A hypopyon may be present. Unlike bacterial keratitis, an epithelial defect may or may not be present. Corneal scrapings should be cultured on media suitable for fungi whenever the history or corneal appearance is suggestive of fungal disease. Diagnosis is often delayed and treatment is difficult, commonly requiring 6 months or longer for severe disease. Natamycin 5%, amphotericin 0.1–0.5%, and voriconazole 0.2–1% are the most frequently used topical agents (Table 7–2). Systemic azoles are probably not helpful unless there is scleritis or intraocular infection. Corneal grafting is often required.

Donovan C et al. Fungal keratitis: mechanisms of infection and management strategies. Surv Ophthalmol. 2021 Aug 20. [Epub ahead of print] [PMID: 34425126]

5. Amoebic Keratitis

Amoebic infection, usually due to *Acanthamoeba*, is an important cause of keratitis. The two greatest risk factors in developed countries are contact lens wear and fresh-water or hot-tub exposure. Although severe pain with perineural and ring infiltrates in the corneal stroma is characteristic, it is not specific and earlier forms with changes confined to the corneal epithelium are identifiable. Diagnosis is facilitated by confocal microscopy and Giemsa staining of cornea smears. Culture requires specialized media. Intensive topical compounded biguanide (polyhexamethylene or chlorhexidine) is initiated immediately, and long-term treatment is required. Diamidine (propamidine or hexamidine) may be added. Oral miltefosine is FDA approved for the treatment of *Acanthamoeba* keratitis, but indications and efficacy have yet to be established. There should be close monitoring for systemic toxicity (vomiting, diarrhea, elevation of transaminases, and kidney function studies) during its use. Delayed diagnosis and prior treatment with topical corticosteroids adversely affect the visual outcome. Corneal grafting may be required after resolution of infection to restore vision. If there is scleral involvement, systemic anti-inflammatory and immunosuppressant medication is helpful in controlling pain, but the prognosis is poor.

Alsoudi AF…Seitzman GD et al. Comparison of two confocal microscopes for diagnosis of acanthamoeba keratitis. Eye (Lond). 2021;35:2061. [PMID: 32760010]
Carrijo-Carvalho LC et al. Therapeutic agents and biocides for ocular infections by free-living amoebae of *Acanthamoeba* genus. Surv Ophthalmol. 2017;62:203. [PMID: 27836717]

ACUTE ANGLE-CLOSURE GLAUCOMA

ESSENTIALS OF DIAGNOSIS

- Older age group, particularly farsighted individuals.
- Rapid onset of severe pain and profound visual loss with "halos around lights."
- Red eye, cloudy cornea, dilated pupil.
- Hard eye on palpation.

General Considerations

Primary acute angle-closure glaucoma (acute angle-closure crisis) results from closure of a preexisting narrow anterior chamber angle. The predisposing factors are shallow anterior chamber, which may be associated with farsightedness or a small eye (short axial length); enlargement of the crystalline lens with age; and inheritance, such as among Inuits and Asians. Closure of the angle is precipitated by pupillary dilation and thus can occur from sitting in a darkened theater, during times of stress, following nonocular administration of anticholinergic or sympathomimetic agents (eg, nebulized bronchodilators, atropine, antidepressants, bowel or bladder antispasmodics, nasal decongestants, or tocolytics), or, rarely,

from pharmacologic mydriasis (see Precautions in Management of Ocular Disorders, below). Subacute primary angle-closure glaucoma may present as recurrent headache.

Secondary acute angle-closure glaucoma, for which the mechanism may differ between cases, does not require a preexisting narrow angle. Secondary acute angle-closure glaucoma may occur in anterior uveitis, with dislocation of the lens, with hemodialysis, or due to various drugs (see Adverse Ocular Effects of Systemic Drugs, below). The reduction in serum osmolarity that occurs with hemodialysis causes an osmotic gradient between the plasma and aqueous fluid, leading to a buildup of fluid in the aqueous compartment. Patients with a compromised outflow system (as with narrow angle) cannot accommodate the buildup and the intraocular pressure rises. Symptoms are the same as in primary acute angle-closure glaucoma, but differentiation is important because of differences in management.

Clinical Findings

Patients with acute glaucoma usually seek treatment immediately because of extreme pain and blurred vision, though there are subacute cases. Typically, the blurred vision is associated with halos around lights. Nausea and abdominal pain may occur. The eye is red, the cornea cloudy, and the pupil moderately dilated and nonreactive to light. Intraocular pressure is usually over 50 mm Hg, producing a hard eye on palpation.

Differential Diagnosis

Acute glaucoma must be differentiated from conjunctivitis, acute uveitis, and corneal disorders (Table 7–1).

Treatment

Initial treatment, regardless of mechanism, is reduction of intraocular pressure. A single 500-mg intravenous dose of acetazolamide, followed by 250 mg orally four times a day, together with topical medications that lower intraocular pressure is usually sufficient. Osmotic diuretics, such as oral glycerin and intravenous urea or mannitol—the dosage of all three being 1–2 g/kg—may be necessary if there is no response to acetazolamide. Definitive treatment depends on the mechanism.

A. Primary Angle-Closure Glaucoma

In primary acute angle-closure glaucoma, once the intraocular pressure has started to fall, topical 4% pilocarpine, 1 drop every 15 minutes for 1 hour and then four times a day, is used to reverse the underlying angle closure. The definitive treatment is cataract extraction, which is becoming more of a first-line treatment. Laser peripheral iridotomy is also still accepted as a first-line treatment.

All patients with primary acute angle closure should undergo prophylactic laser peripheral iridotomy to the unaffected eye, or early cataract extraction should be considered, unless that eye has already undergone cataract or glaucoma surgery.

B. Secondary Angle-Closure Glaucoma

In secondary acute angle-closure glaucoma, additional treatment is determined by the cause.

Prognosis

Untreated acute angle-closure glaucoma results in severe and permanent visual loss within 2–5 days after onset of symptoms. Affected patients need to be monitored for development of chronic glaucoma.

When to Refer

Any patient with suspected acute angle-closure glaucoma must be referred emergently to an ophthalmologist.

Prum BE Jr et al. Primary Angle Closure Preferred Practice Pattern(®) Guidelines. Ophthalmology. 2016;123:P1. [PMID: 26581557]

Tanner L et al. Has the EAGLE landed for the use of clear lens extraction in angle-closure glaucoma? And how should primary angle-closure suspects be treated? Eye (Lond). 2020;34:40. [PMID: 31649349]

CHRONIC GLAUCOMA

ESSENTIALS OF DIAGNOSIS

- Three types of chronic glaucoma: open-angle glaucoma, angle-closure glaucoma, and normal-tension glaucoma.
- No symptoms in early stages.
- Insidious progressive bilateral loss of peripheral vision resulting in tunnel vision; visual acuities preserved until advanced disease.
- Pathologic cupping of the optic disks.
- Intraocular pressure is usually elevated.

General Considerations

Chronic glaucoma is characterized by gradually progressive excavation ("cupping") of the optic disk with loss of vision progressing from slight visual field loss to complete blindness. In **chronic open-angle glaucoma,** primary or secondary, intraocular pressure is elevated due to reduced drainage of aqueous fluid through the trabecular meshwork. In **chronic angle-closure glaucoma,** which is particularly common in Inuits and eastern Asians, flow of aqueous fluid into the anterior chamber angle is obstructed. In **normal-tension glaucoma,** intraocular pressure is not elevated but the same pattern of optic nerve damage occurs.

Primary chronic open-angle glaucoma is usually bilateral. There is an increased prevalence in first-degree relatives of affected individuals and in diabetic patients. In Afro-Caribbean and African persons, and probably in Hispanic persons, it is more frequent, occurs at an earlier

age, and results in more severe optic nerve damage. Secondary chronic open-angle glaucoma may result from ocular disease, eg, pigment dispersion, pseudoexfoliation, uveitis, or trauma; or corticosteroid therapy, whether it is intraocular, topical, inhaled, intranasal, or systemic.

In the United States, it is estimated that 2% of people over 40 years of age have glaucoma, affecting over 2.5 million individuals. At least 25% of cases are undetected. Over 90% of cases are of the open-angle type. Worldwide, about 45 million people have open-angle glaucoma, of whom about 4.5 million are bilaterally blind. About 4 million people, of whom approximately 50% live in China, are bilaterally blind from chronic angle-closure glaucoma.

Clinical Findings

Because initially there are no symptoms, chronic glaucoma is often first suspected at a routine eye test. Diagnosis requires consistent and reproducible abnormalities in at least two of three parameters—optic disk or retinal nerve fiber layer (or both), visual field, and intraocular pressure.

1. Optic disk cupping—Optic disk cupping is identified as an absolute increase or an asymmetry between the two eyes of the ratio of the diameter of the optic cup to the diameter of the whole optic disk (cup-disk ratio). (Cup-disk ratio greater than 0.5 or asymmetry between eyes of 0.2 or more is suggestive.) Detection of optic disk cupping and associated abnormalities of the retinal nerve fiber layer is facilitated by optical coherence tomography scans.

2. Visual field abnormalities—Visual field abnormalities initially develop in the paracentral region, followed by constriction of the peripheral visual field. Central vision remains good until late in the disease.

3. Intraocular pressure—The normal range of intraocular pressure is 10–21 mm Hg. In many individuals (about 4.5 million in the United States), elevated intraocular pressure is not associated with optic disk or visual field abnormalities (ocular hypertension). Monitoring for the development of glaucoma is required in all such cases; a significant proportion of eyes with primary open-angle glaucoma have normal intraocular pressure when it is first measured, and only repeated measurements identify the abnormally high pressure. In normal-tension glaucoma, intraocular pressure is always within the normal range.

Prevention

There are many causes of optic disk abnormalities or visual field changes that mimic glaucoma, and visual field testing may prove unreliable in some patients, particularly in the older age group. Hence, the diagnosis of glaucoma is not always straightforward and screening programs need to involve eye care professionals.

Although all persons over age 50 years may benefit from intraocular pressure measurement and optic disk examination every 3–5 years, screening for chronic open-angle glaucoma should be targeted at individuals with an affected first-degree relative, at persons who have diabetes mellitus, and at older individuals with African or Hispanic ancestry. Screening may also be warranted in patients taking long-term oral or combined intranasal and inhaled corticosteroid therapy. Screening for chronic angle-closure glaucoma should be targeted at Inuits and Asians.

Treatment

A. Medications

Medical treatment is directed toward lowering intraocular pressure, even with normal-tension glaucoma. Prostaglandin analog eye drops are commonly used as first-line therapy because of their efficacy, lack of systemic side effects, and convenient once-daily dose (except unoprostone) (see Table 7–2 for medications, doses, and side effects). All may produce conjunctival hyperemia, permanent darkening of the iris and eyebrow color, increased eyelash growth, and reduction of periorbital fat (prostaglandin-associated periorbitopathy). Latanoprostene bunod is metabolized into latanoprost and another component that releases nitric oxide, which increases trabecular outflow. Topical beta-adrenergic blocking agents may be used alone or in combination with a prostaglandin analog. They may be contraindicated in patients with reactive airway disease or heart failure. Cardioselective betaxolol is theoretically safer in reactive airway disease but less effective at reducing intraocular pressure. Brimonidine 0.2%, a selective alpha-2-agonist, and topical carbonic anhydrase inhibitors also can be used in addition to a prostaglandin analog or a beta-blocker or as initial therapy when prostaglandin analogs and beta-blockers are contraindicated. All three are associated with allergic reactions. Brimonidine may cause uveitis. Apraclonidine, 0.5–1%, another alpha-2-agonist, can be used to defer the need for surgery in patients receiving maximal medical therapy, but long-term use is limited by adverse reactions. It is more commonly used to control acute rise in intraocular pressure, such as after laser therapy. The topical agent netarsudil ophthalmic solution 0.02% (a Rho kinase inhibitor) increases aqueous fluid outflow through the trabecular meshwork. Pilocarpine 1–4% is rarely used because of adverse effects. Oral carbonic anhydrase inhibitors (acetazolamide, methazolamide, and dichlorphenamide) may be used on a long-term basis if topical therapy is inadequate and surgical or laser therapy is inappropriate.

Various eye drop preparations combining two agents (eg, prostaglandin analogs, beta-adrenergic blocking agents, brimonidine, and topical carbonic anhydrase inhibitors) are available to improve compliance when multiple medications are required. Formulations of one or two agents without preservative or not including benzalkonium chloride as the preservative are preferred to reduce adverse ocular effects for patients with allergies or severe dry eyes.

B. Laser Therapy and Surgery

1. Open-angle glaucoma—Laser trabeculoplasty is used as an adjunct to topical therapy to defer surgery for open-angle glaucoma; it is also advocated as primary treatment,

especially when compliance with medications is an issue. Surgery is generally undertaken when intraocular pressure is inadequately controlled by medical and laser therapy, but it may also be used as primary treatment in advanced cases. Trabeculectomy remains the standard procedure. Adjunctive treatment with subconjunctival mitomycin or fluorouracil is used perioperatively or postoperatively in worse prognosis cases. A variety of less invasive procedures that avoid a full-thickness incision into the eye, called microinvasive glaucoma surgery, are appropriate for moderate glaucoma and are associated with fewer complications but can be more difficult to perform.

2. Angle-closure glaucoma—In chronic angle-closure glaucoma, laser peripheral iridotomy, surgical peripheral iridectomy, or cataract extraction may be helpful. In patients with asymptomatic narrow anterior chamber angles, which includes about 10% of Chinese adults, prophylactic laser peripheral iridotomy can be performed to reduce the risk of acute and chronic angle-closure glaucoma. However, there are concerns about the efficacy of such treatment and the risk of cataract progression and corneal decompensation. In the United States, about 1% of people over age 35 years have narrow anterior chamber angles, but acute and chronic angle closure are sufficiently uncommon that prophylactic therapy is not generally advised.

3. Normal-tension glaucoma—The goal of treatment for normal-tension glaucoma is reduction in intraocular pressure (even if it is in the normal range) to prevent progression. As with open-angle glaucoma, if intraocular pressure is not lowered with medical therapy alone, laser trabeculoplasty is used as an adjunct. Trabeculectomy is the standard surgical procedure if medical and laser therapy are inadequate.

Prognosis

Untreated chronic glaucoma that begins at age 40–45 years will probably cause complete blindness by age 60–65. Early diagnosis and treatment can preserve useful vision throughout life. In primary open-angle glaucoma and if treatment is required in ocular hypertension, the aim is to reduce intraocular pressure to a level that will adequately reduce progression of visual field loss. In eyes with marked visual field or optic disk changes, intraocular pressure must be reduced to less than 16 mm Hg. In normal-tension glaucoma with progressive visual field loss, it is necessary to achieve even lower intraocular pressure such that surgery is often required.

When to Refer

All patients with suspected chronic glaucoma should be referred to an ophthalmologist.

Jonas JB et al. Glaucoma. Lancet. 2017;390:2183. [PMID: 28577860]
Prum BE Jr et al. Primary open-angle glaucoma Preferred Practice Pattern(®) guidelines. Ophthalmology. 2016;123:P41. [PMID: 26581556]
Schehlein EM et al. New classes of glaucoma medications. Curr Opin Ophthalmol. 2017;28:161. [PMID: 27828896]
Stein JD et al. Glaucoma in adults—screening, diagnosis, and management: a review. JAMA. 2021;325:164. [PMID: 33433580]

UVEITIS

ESSENTIALS OF DIAGNOSIS

- Usually immunologic but possibly infective or neoplastic.
- Inflammation may be confined to the eye or may be systemic.
- **Acute anterior uveitis:** sudden redness and blurry vision often with photophobia.
- **Posterior uveitis:** gradual loss of vision, commonly with floaters, in a variably inflamed eye.

General Considerations

Intraocular inflammation (uveitis) is classified as acute or chronic and as nongranulomatous or granulomatous, according to the clinical signs, and by its involvement of the anterior, intermediate, posterior, or all (panuveitis) segments of the eye.

In most cases the pathogenesis of uveitis is primarily immunologic, but infection may be the cause, particularly in immunodeficiency states. The systemic disorders associated with acute nongranulomatous anterior uveitis are the HLA-B27-related conditions (ankylosing spondylitis, reactive arthritis, psoriasis, ulcerative colitis, and Crohn disease). Chronic nongranulomatous anterior uveitis occurs in juvenile idiopathic arthritis. Behçet syndrome produces both anterior uveitis, with recurrent hypopyon, and posterior uveitis, characteristically with branch retinal vein occlusions. Both herpes simplex and herpes zoster infections may cause nongranulomatous and granulomatous anterior uveitis as well as retinitis (acute retinal necrosis).

Diseases producing granulomatous anterior uveitis also tend to be causes of posterior uveitis. These include sarcoidosis, toxoplasmosis, tuberculosis, syphilis, Vogt-Koyanagi-Harada disease (bilateral uveitis associated with alopecia, poliosis [depigmented eyelashes, eyebrows, or hair], vitiligo, and hearing loss), and sympathetic ophthalmia that occurs after penetrating ocular trauma. In toxoplasmosis, there may be evidence of previous episodes of retinochoroiditis. Syphilis characteristically produces a "salt and pepper" fundus but may present with a wide variety of clinical manifestations. The principal pathogens responsible for ocular inflammation in HIV infection are cytomegalovirus (CMV), herpes simplex and herpes zoster viruses, mycobacteria, *Cryptococcus, Toxoplasma,* and *Candida*.

Retinal vasculitis and intermediate uveitis predominantly manifest as posterior uveitis with central or peripheral retinal abnormalities in retinal vasculitis and far peripheral retinal abnormalities (pars planitis) in

intermediate uveitis. Retinal vasculitis can be caused by a wide variety of infectious agents and noninfectious systemic conditions but also may be idiopathic. Intermediate uveitis is often idiopathic but can be due to multiple sclerosis or sarcoidosis.

Clinical Findings

Anterior uveitis is characterized by inflammatory cells and flare within the aqueous. In severe cases, there may be hypopyon (layered collection of white cells) and fibrin within the anterior chamber. Cells may also be seen on the corneal endothelium as keratic precipitates. In granulomatous uveitis, there are large "mutton-fat" keratic precipitates, and sometimes iris nodules. In nongranulomatous uveitis, the keratic precipitates are smaller or absent with no iris nodules. The pupil is usually small, and with the development of posterior synechiae (adhesions between the iris and anterior lens capsule), it also becomes irregularly shaped and poorly reactive.

Nongranulomatous anterior uveitis tends to present acutely with unilateral pain, redness, photophobia, and visual loss. However, the ocular inflammation associated with juvenile idiopathic arthritis is frequently indolent, commonly asymptomatic initially, and carries a high risk of sight-threatening complications. Granulomatous anterior uveitis is also frequently chronic, recurrent, and indolent, causing blurred vision in a variably inflamed eye.

In **posterior uveitis,** there are cells in the vitreous and there may be inflammatory retinal or choroidal lesions. New retinal lesions are yellow with indistinct margins and there may be retinal hemorrhages. Older lesions have more defined margins and are commonly pigmented. Retinal vessel sheathing may occur adjacent to such lesions or more diffusely. In severe cases, vitreous opacity precludes visualization of retinal details.

Posterior uveitis can be unilateral or bilateral with symptoms of floaters and visual loss. Symptoms are commonly slower in onset, though acute presentations can occur. Visual loss may be due to vitreous haze and opacities, inflammatory lesions involving the macula, macular edema, retinal vein occlusion, or rarely, optic neuropathy.

Differential Diagnosis

Retinal detachment, intraocular tumors, and CNS lymphoma may all masquerade as uveitis.

Treatment

Anterior uveitis usually responds to topical corticosteroids. Occasionally, periocular or intraocular corticosteroid injections or even systemic corticosteroids are required. Dilation of the pupil is important to relieve discomfort and prevent permanent posterior synechiae. **Posterior uveitis** more commonly requires systemic, periocular, or intravitreal corticosteroid therapy. In chronic cases, systemic corticosteroid-sparing immunomodulatory therapy with agents such as azathioprine, cyclosporine, mycophenolate, methotrexate, tacrolimus, or sirolimus is commonly required. Biologic therapies are also often used. Pupillary dilation is not usually necessary.

If an infectious cause is identified, specific antimicrobial therapy is often needed. In general, the prognosis for anterior uveitis, particularly the nongranulomatous type, is better than for posterior uveitis.

When to Refer

- Any patient with suspected acute uveitis should be referred urgently to an ophthalmologist or emergently if visual loss or pain is severe.
- Any patient with suspected chronic uveitis should be referred to an ophthalmologist, urgently if there is more than mild visual loss.

When to Admit

Patients with severe uveitis, particularly those requiring intravenous therapy, may require hospital admission.

Al-Janabi A et al. Long-term outcomes of treatment with biological agents in eyes with refractory, active, noninfectious intermediate uveitis, posterior uveitis, or panuveitis. Ophthalmology. 2020;127:410. [PMID: 31607412]

Jabs DA. Immunosuppression for the uveitides. Ophthalmology. 2018;125:193. [PMID: 28942074]

Krishna U et al. Uveitis: a sight-threatening disease which can impact all systems. Postgrad Med J. 2017;93:766. [PMID: 28942431]

Rathinam SR et al; FAST Research Group. Effect of corticosteroid-sparing treatment with mycophenolate mofetil vs methotrexate on inflammation in patients with uveitis: a randomized clinical trial. JAMA. 2019;322:936. [PMID: 31503307]

Sève P et al. Uveitis: diagnostic work-up. A literature review and recommendations from an expert committee. Autoimmun Rev. 2017;16:1254. [PMID: 29037906]

CATARACT

ESSENTIALS OF DIAGNOSIS

- Gradually progressive blurred vision.
- No pain or redness.
- Lens opacities (may be grossly visible).

General Considerations

Cataracts are opacities of the crystalline lens and are usually bilateral. They are the leading cause of blindness worldwide. Age-related cataract is by far the most common cause. Other causes include (1) congenital (from intrauterine infections, such as rubella and CMV, or inborn errors of metabolism, such as galactosemia); (2) traumatic; (3) secondary to systemic disease (diabetes mellitus, myotonic dystrophy, atopic dermatitis); (4) topical, systemic, or inhaled corticosteroid treatment; (5) uveitis; or

(6) radiation exposure. Most persons over age 60 have some degree of lens opacity. Cigarette smoking increases the risk of cataract formation. Multivitamin/mineral supplements and high dietary antioxidants may prevent the development of age-related cataract.

Clinical Findings

The predominant symptom is progressive blurring of vision. Glare, especially in bright light or with night driving; change of focusing, particularly development of nearsightedness; and monocular double vision may occur.

Even in its early stages, a cataract can be seen through a dilated pupil with an ophthalmoscope or slit lamp. As the cataract matures, the retina will become increasingly difficult to visualize, until finally the fundus reflection is absent and the pupil is white.

Treatment

Functional visual impairment, specifically its effect on daily activities and increased risk of falls, is the prime criterion for surgery. The cataract is usually removed by one of the techniques in which the posterior lens capsule remains (extracapsular), thus providing support for a prosthetic intraocular lens. Ultrasonic fragmentation (phacoemulsification) of the lens nucleus and foldable intraocular lenses allow cataract surgery to be performed through a small incision without the need for sutures, thus reducing the postoperative complication rate and accelerating visual rehabilitation. The standard monofocal prosthetic intraocular lens can correct near or far vision. Premium intraocular lenses (multifocal, extended depth of focus, and accommodative) reduce the need for both distance and near vision correction. In the developing world, manual small-incision surgery, in which the lens nucleus is removed intact, is popular because less equipment is required. Additional laser treatment may be required subsequently (months to years after the initial cataract surgery) if the posterior capsule opacifies. The use of topical eye drops to dissolve or prevent cataracts has shown promising results in experimental models; surgery, however, is currently the only treatment option for a visually significant cataract.

Prognosis

Cataract surgery is cost-effective in improving survival and quality of life. In the developed world, it improves visual acuity in 95% of cases. In the other 5%, there is preexisting retinal damage or operative or postoperative complications. In less developed areas, the improvement in visual acuity is not as high, in part due to uncorrected refractive error postoperatively. A large number of drugs, such as alpha-adrenoreceptor antagonists for benign prostatic hyperplasia or systemic hypertension and antipsychotics, increase the risk of complications during surgery (floppy iris syndrome) and in the early postoperative period. Nasolacrimal duct obstruction increases the risk of intraocular infection (endophthalmitis).

The alpha-blocker tamsulosin has been shown to have the greatest risk of floppy iris syndrome. There is no consensus about whether to stop alpha-blockers before surgery because the effects of the drug on the iris can persist for months to years. The surgeon must know if the patient is taking an alpha-blocker to prepare for iris issues during surgery. If the patient has not yet started an alpha-blocker and is planning to have cataract surgery shortly, it is best to wait until after surgery to begin the medication, if possible.

When to Refer

Patients with cataracts should be referred to an ophthalmologist when their visual impairment adversely affects their everyday activities.

Enright JM et al. Floppy iris syndrome and cataract surgery. Curr Opin Ophthalmol. 2017;28:29. [PMID: 27653607]
Lian RR et al. The quest for homeopathic and nonsurgical cataract treatment. Curr Opin Ophthalmol. 2020;31:61. [PMID: 31770163]
Nanji KC et al. Preventing adverse events in cataract surgery: recommendations from a Massachusetts expert panel. Anesth Analg. 2018;126:1537. [PMID: 28991115]
Rampat R et al. Multifocal and extended depth-of-focus intraocular lenses in 2020. Ophthalmology. 2021;128:e164. [PMID: 32980397]

RETINAL DETACHMENT

ESSENTIALS OF DIAGNOSIS

- Loss of vision in one eye that is usually rapid, possibly with "curtain" spreading across field of vision.
- No pain or redness.
- Detachment seen by ophthalmoscopy.

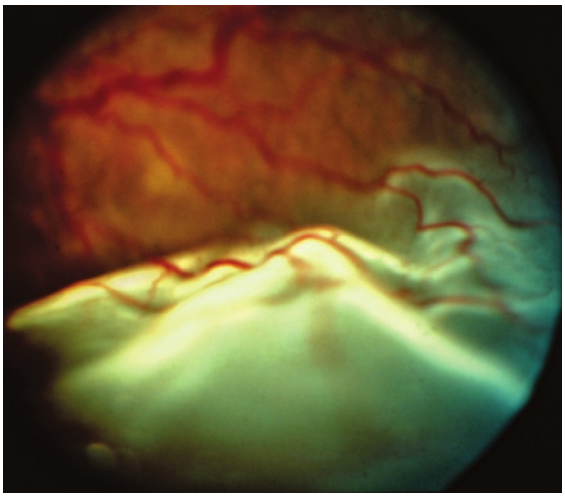
General Considerations

Most cases of retinal detachment are due to development of one or more peripheral retinal tears or holes (rhegmatogenous retinal detachment). This usually results from posterior vitreous detachment, related to degenerative changes in the vitreous, and often occurs in persons over 50 years of age. Nearsightedness and cataract extraction are the two most common predisposing causes. It may also be caused by penetrating or blunt ocular trauma, sometimes years earlier.

Tractional retinal detachment occurs when there is preretinal fibrosis, such as in proliferative retinopathy due to diabetic retinopathy or retinal vein occlusion, or as a complication of rhegmatogenous retinal detachment. Exudative retinal detachment results from accumulation of subretinal fluid, such as in neovascular age-related macular degeneration or secondary to choroidal tumor.

Clinical Findings

Rhegmatogenous retinal detachment usually starts in the peripheral retina, spreading rapidly to cause visual field loss. Symptoms of the predisposing posterior vitreous



▲ **Figure 7–1.** Inferior retinal detachment as seen on direct or indirect ophthalmoscopy.

detachment with vitreo-retinal traction include recent onset of or increase in floaters (moving spots or strands like cobwebs in the visual field) and photopsias (flashes of light). Central vision remains intact until the central macula becomes detached. On ophthalmoscopic examination, the retina may be seen elevated in the vitreous cavity with an irregular surface (Figure 7–1). In tractional retinal detachment, there is irregular retinal elevation adherent to scar tissue on the retinal surface, sometimes extending into the vitreous. Exudative retinal detachments are dome-shaped and the subretinal fluid shifts position with changes in posture. Ocular ultrasonography assists the detection and characterization of retinal detachment.

Treatment

Treatment of rhegmatogenous retinal detachments requires closing all the retinal tears and holes by forming a permanent adhesion between the neurosensory retina, the retinal pigment epithelium, and the choroid with laser photocoagulation to the retina or cryotherapy to the sclera. Certain types of uncomplicated retinal detachment may be treated by pneumatic retinopexy, in which an expansile gas is injected into the vitreous cavity and the patient's head is positioned to facilitate apposition between the gas and the hole, which permits reattachment of the retina. Once the retina is reattached, the retinal defects are surrounded by laser photocoagulation or cryotherapy scars; these two methods are also used to seal retinal defects without associated detachment.

In complicated retinal detachments, particularly tractional retinal detachments, retinal reattachment can be accomplished only by vitrectomy, direct manipulation of the retina, and internal tamponade of the retina with air, expansile gas, or silicone oil. The presence of an expansile gas within the eye is a contraindication to air travel, mountaineering at high altitude, and nitrous oxide anesthesia, all of which can cause the gas to expand with severe increases in intraocular pressure. Such gases persist in the globe for weeks after surgery. (See Chapter 37.) Treatment of exudative retinal detachments is determined by the underlying cause.

Prognosis

About 90% of uncomplicated rhegmatogenous retinal detachments can be cured with one operation. The visual prognosis is worse if the macula is detached or if the detachment is of long duration.

When to Refer

All cases of retinal detachment must be referred urgently to an ophthalmologist, and emergently if central vision is good because this indicates that the macula has not yet detached. During transportation, the patient's head is positioned so that the retinal tear is placed at the lowest point of the eye to minimize extension of the detached retina. If the inferior retina is detached, the patient should keep the head upright so that the tear is located at the lowest point, whereas if the temporal retina is detached, the patient should keep the temporal side of the head down to reduce the chances that the fluid will extend beneath the central retina, causing the macula to detach. If vision is good and the macula is attached, patients should minimize eye motion; in some patients, patching both eyes can be helpful in preventing the eyes from moving rapidly around until surgery can be performed to repair the retinal detachment.

Lahham S et al. Role of point of care ultrasound in the diagnosis of retinal detachment in the emergency department. Open Access Emerg Med. 2019;11:265. [PMID: 32009820]

Sultan ZN et al. Rhegmatogenous retinal detachment: a review of current practice in diagnosis and management. BMJ Open Ophthalmol. 2020;5:e000474. [PMID: 33083551]

VITREOUS HEMORRHAGE

Patients with vitreous hemorrhage complain of sudden visual loss, abrupt onset of floaters that may progressively increase in severity, or occasionally, "bleeding within the eye." Visual acuity ranges from 20/20 (6/6) to light perception. The eye is not inflamed, red, or painful, and clues to diagnosis are inability to see fundus details or localized blood in the vitreous, in front of the retina. Causes of vitreous hemorrhage include retinal tear (with or without detachment), diabetic or sickle cell retinopathy, retinal vein occlusion, retinal vasculitis, neovascular age-related macular degeneration, retinal arterial macroaneurysm, blood dyscrasia, therapeutic anticoagulation, trauma, subarachnoid hemorrhage, and severe straining (Valsalva retinopathy).

When to Refer

All patients with suspected vitreous hemorrhage must be referred urgently to an ophthalmologist to determine the etiology. If the vitreous hemorrhage is caused by a retinal tear or detachment, it must be repaired urgently to prevent permanent vision loss.

Manandhar LD et al. Clinical profile and management of vitreous hemorrhage in tertiary eye care centre in Nepal. Nepal J Ophthalmol. 2020;12:99. [PMID: 32799245]
Propst SL et al. Ocular point-of-care ultrasonography to diagnose posterior chamber abnormalities: a systematic review and meta-analysis. JAMA Netw Open. 2020;3:e1921460. [PMID: 32074291]

AGE-RELATED MACULAR DEGENERATION

ESSENTIALS OF DIAGNOSIS

- Older age group.
- In one or both eyes; acute or chronic deterioration of central vision; distortion or abnormal size of images, sometimes developing acutely.
- No pain or redness.
- Classified as dry ("atrophic," "geographic") or wet ("neovascular," "exudative") macular degeneration.
- Macular abnormalities seen by ophthalmoscopy.

General Considerations

Age-related macular degeneration is the leading cause of permanent visual loss in the older population. Its prevalence progressively increases over age 50 years (to almost 30% by age 75). Its occurrence and response to treatment are likely influenced by genetically determined variations, many of which involve the complement pathway. Other associated factors are sex (slight female predominance), family history, hypertension, hypercholesterolemia, cardiovascular disease, farsightedness, light iris color, and cigarette smoking (the most readily modifiable risk factor).

Although both dry and wet age-related macular degeneration are progressive and usually bilateral, they differ in manifestations, prognosis, and management.

Clinical Findings

Drusen are the hallmark of age-related macular degeneration. Hard drusen appear ophthalmoscopically as discrete yellow subretinal deposits. Soft drusen are paler and less distinct. Large, confluent soft drusen are risk factors for neovascular (wet) age-related macular degeneration. Vision loss in age-related macular degeneration involves the central vision only in most patients. Peripheral fields, and hence navigational vision, are maintained, except in patients with severe neovascular age-related macular degeneration.

"Dry" age-related macular degeneration is characterized by gradually progressive bilateral visual loss due to geographic atrophy of the outer retina, the retinal pigment epithelium, and the choriocapillaris, which supplies blood to both the outer retina and the retinal pigment epithelium. In **"wet" age-related macular degeneration**, choroidal new vessels grow under either the retina or the retinal pigment epithelial cells, leading to accumulation of exudative fluid, hemorrhage, and fibrosis. The onset of visual loss is more rapid and more severe than in atrophic degeneration. The two eyes are frequently affected sequentially over a period of a few years. Although "dry" age-related macular degeneration is much more common, untreated "wet" age-related macular degeneration accounts for about 90% of all cases of legal blindness due to age-related macular degeneration.

Treatment

No dietary modification has been shown to prevent the development of age-related macular degeneration, but its progression may be reduced by oral treatment with antioxidants (vitamins C and E), zinc, copper, and carotenoids (lutein and zeaxanthin, rather than vitamin A [beta-carotene]). Oral omega-3 fatty acids do not provide additional benefit.

There is no specific treatment for dry age-related macular degeneration but, as for wet degeneration, rehabilitation including low-vision aids is important. In addition, patients should be advised to stop smoking and to take vitamin supplements as described above.

In wet age-related macular degeneration, inhibitors of vascular endothelial growth factors (VEGF), such as ranibizumab, bevacizumab, aflibercept, and brolucizumab, can cause regression of choroidal neovascularization with resorption of subretinal fluid and improvement or stabilization of vision. Long-term repeated intraocular injections are required and must be administered in the eye clinic several times a year, if not monthly. Treatment is well tolerated with minimal adverse effects, but there is a risk of infection (1/2000), retinal detachment (1/10,000), vitreous hemorrhage, and cataract. Brolucizumab has been associated with intraocular inflammation and occlusive retinal vasculitis resulting in irreversible vision loss in some patients. A certain percentage of patients do not respond to anti-VEGF injections and up to one-third of eyes lose vision despite regular treatment.

When to Refer

Older patients with sudden visual loss, particularly paracentral or central distortion or scotoma with preserved central acuity, should be referred urgently to an ophthalmologist.

Baumal CR et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of brolucizumab. Ophthalmology. 2020;127:1345. [PMID: 32344075]
Cabral de Guimaraes TA et al. Treatments for dry age-related macular degeneration: therapeutic avenues, clinical trials and future directions. Br J Ophthalmol. 2022;106:297. [PMID: 33741584]
Plyukhova AA et al. Comparative safety of bevacizumab, ranibizumab and aflibercept for treatment of neovascular age-related macular degeneration (AMD): a systematic review and network meta-analysis of direct comparative studies. J Clin Med. 2020;9:1522. [PMID: 32443612]

CENTRAL & BRANCH RETINAL VEIN OCCLUSIONS

ESSENTIALS OF DIAGNOSIS

- Sudden monocular loss of vision.
- No pain or redness.
- Widespread or sectoral retinal hemorrhages.

General Considerations

Central and branch retinal vein occlusion are common causes of acute vision loss, with branch vein occlusions being four times more common. The major predisposing factors are the etiologic factors associated with arteriosclerosis, but glaucoma is also a major risk factor.

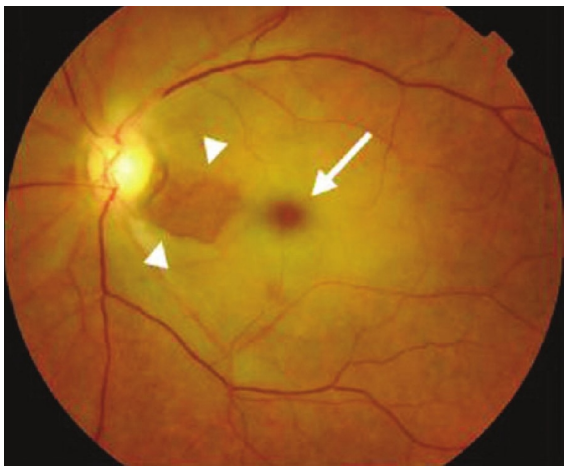
Clinical Findings

A. Symptoms and Signs

Ophthalmoscopic signs of **central retinal vein occlusion** include widespread retinal hemorrhages, retinal venous dilation and tortuosity, retinal cotton-wool spots, and optic disk swelling (Figure 7–2). Rarely, central retinal vein occlusion presents with severe vision loss and pain when neovascularization of the iris develops, usually about 90 days after a central retinal vein occlusion has caused severe retinal nonperfusion.

Branch retinal vein occlusion may present in a variety of ways. Sudden loss of vision may occur at the time of occlusion if the fovea is involved, or some time afterward from vitreous hemorrhage due to retinal new vessels. More gradual visual loss may occur with development of macular edema. In acute branch retinal vein occlusion, the retinal abnormalities (hemorrhages, microaneurysms, venous dilation and tortuosity, and cotton-wool spots) are confined to the area drained by the obstructed vein.

To assess for possible reversible risk factors, check blood pressure and ask about tobacco smoking in all patients, and ask women about estrogen therapy (including combined oral contraceptives). Patients should also be asked about a history of glaucoma and should undergo a comprehensive eye examination to check intraocular pressure and for signs of open- or narrow-angle glaucoma.



▲ **Figure 7–2.** Acute central retinal artery occlusion with cherry-red spot (arrow) seen at the fovea centered in macular loss of retinal transparency, and preserved retinal perfusion (arrowheads) adjacent to the optic disk due to macular cilioretinal artery supply. (Reproduced, with permission, from Riordan-Eva P, Augsburger JJ. *Vaughan & Asbury's General Ophthalmology*, 19th ed. McGraw Hill, 2018.)

B. Laboratory Findings

Obtain screening laboratory studies for diabetes mellitus, hyperlipidemia, and hyperviscosity (especially in simultaneous bilateral disease), including serum protein electrophoresis for paraproteinemia. Particularly in younger patients, consider obtaining antiphospholipid antibodies, lupus anticoagulant, tests for inherited thrombophilia, and plasma homocysteine levels.

Complications

If central retinal vein occlusion is associated with widespread retinal ischemia, manifesting as poor visual acuity (20/200 [6/60] or worse), florid retinal abnormalities, an afferent pupillary defect, and extensive areas of capillary closure on fluorescein angiography, there is a high risk of development of neovascular (rubeotic) glaucoma, typically within the first 3 months after the occlusion. Branch retinal vein occlusion may be complicated by peripheral retinal neovascularization or chronic macular edema.

Treatment

A. Macular Edema

Intravitreal injection of VEGF inhibitors, including ranibizumab, bevacizumab, or aflibercept, is beneficial in patients with macular edema due to either branch or central retinal vein occlusion. Intravitreal triamcinolone improves vision in chronic macular edema due to nonischemic central retinal vein occlusion, whereas an intravitreal implant containing dexamethasone is beneficial in both central and branch retinal vein occlusion. However, intraocular corticosteroids carry the risk of glaucoma in 20–65% of patients and will cause cataract in all patients who have not already had cataract surgery. Retinal laser photocoagulation may be indicated in chronic macular edema due to branch, but not central, retinal vein occlusion, but most patients are treated with VEGF inhibitor injections rather than laser.

B. Neovascularization

Eyes at risk for neovascular glaucoma following ischemic central retinal vein occlusion can be treated with panretinal laser photocoagulation prophylactically or as soon as there is evidence of neovascularization, with the latter approach necessitating frequent monitoring. Regression of retinal and iris neovascularization can be achieved with

intravitreal injections of bevacizumab or other anti-VEGF agents. In branch retinal vein occlusion complicated by retinal neovascularization, the ischemic retina should be treated with laser photocoagulation.

Prognosis

In central retinal vein occlusion, severity of visual loss initially is a good guide to visual outcome. Initial visual acuity of 20/60 (6/18) or better indicates a good prognosis. Visual prognosis is poor for eyes with neovascular glaucoma. In branch retinal vein occlusion, visual outcome is determined by the severity of glaucoma and macular damage from hemorrhage, ischemia, or edema.

When to Refer

All patients with retinal vein occlusion should be referred urgently to an ophthalmologist.

Ang JL et al. A systematic review of real-world evidence of the management of macular oedema secondary to branch retinal vein occlusion. Eye (Lond). 2020;34:1770. [PMID: 32313172]
Hykin P et al; LEAVO Study Group. Clinical effectiveness of intravitreal therapy with ranibizumab vs aflibercept vs bevacizumab for macular edema secondary to central retinal vein occlusion: a randomized clinical trial. JAMA Ophthalmol. 2019;137:1256. [PMID: 31465100]
Scott IU et al. Month 24 outcomes after treatment initiation with anti-vascular endothelial growth factor therapy for macular edema due to central retinal or hemiretinal vein occlusion: SCORE2 Report 10: a secondary analysis of the SCORE2 randomized clinical trial. JAMA Ophthalmol. 2018;136:337. [PMID: 29476687]
Shalchi Z et al. Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. Cochrane Database Syst Rev. 2020;7:CD009510. [PMID: 32633861]

CENTRAL & BRANCH RETINAL ARTERY OCCLUSIONS

ESSENTIALS OF DIAGNOSIS

- Sudden monocular loss of vision.
- No pain or redness.
- Widespread or sectoral pale retinal swelling.

General Considerations

Acute retinal arterial ischemia, including central and branch retinal artery occlusion, is a true ocular and medical emergency. In patients 50 years of age or older with central retinal artery occlusion, giant cell arteritis must be considered (see Ischemic Optic Neuropathy and Chapter 20). Otherwise, even if no retinal emboli are identified on ophthalmoscopy, urgent investigation for carotid and cardiac sources of emboli must be undertaken in central and branch retinal artery occlusion so that timely treatment can be given to reduce the risk of stroke (see Chapters 12, 14, and 24). Diabetes mellitus, hyperlipidemia, and systemic hypertension are common etiologic factors. Migraine, oral contraceptives, systemic vasculitis, congenital or acquired thrombophilia, and hyperhomocysteinemia are also causes, particularly in young patients. Internal carotid artery dissection should be considered, especially when there is neck pain or a recent history of neck trauma.

Clinical Findings

A. Symptoms and Signs

Central retinal artery occlusion presents as sudden profound monocular visual loss. Visual acuity is usually reduced to counting fingers or worse, and visual field may be restricted to an island of vision in the temporal field. Ophthalmoscopy reveals pale swelling of the retina with a cherry-red spot at the fovea (Figure 7–2). Occasionally, emboli are seen in the central retinal artery or its branches. The retinal swelling subsides over a period of 4–6 weeks, leaving a pale optic disk with thinning of the inner retina on optical coherence tomography scans; these findings can help diagnose unexplained vision loss if the patient is not examined during the acute occlusive event.

Branch retinal artery occlusion may also present with sudden loss of vision if the fovea is involved, but more commonly sudden loss of a discrete area in the visual field in one eye is the presenting complaint. Fundus signs of retinal swelling and sometimes adjacent cotton-wool spots are limited to the area of retina supplied by the occluded artery.

The clinician should identify risk factors for cardiac sources of emboli including arrhythmia, particularly atrial fibrillation, and cardiac valvular disease, and check the blood pressure. Nonocular clinical features of giant cell arteritis are age 50 years or older, headache, scalp tenderness, jaw claudication, general malaise, weight loss, symptoms of polymyalgia rheumatica, and tenderness, thickening, or absence of pulse of the superficial temporal arteries. Table 20–12 lists the clinical manifestations of vasculitis.

B. Laboratory Findings

Giant cell arteritis should be considered in cases of central retinal artery occlusion without visible emboli. ESR and CRP are usually elevated in giant cell arteritis, but one or both may be normal (see Chapter 20). Consider screening for other types of vasculitis (see Table 20–11). Screen for diabetes mellitus and hyperlipidemia in all patients. Particularly in younger patients, consider testing for antiphospholipid antibodies, lupus anticoagulant, inherited thrombophilia, and elevated plasma homocysteine.

C. Imaging

A brain MRI with diffusion weighted imaging sequences should be obtained urgently to look for cerebral infarction, which is present in up to 31% of patients with branch or central retinal artery occlusion. Obtain duplex ultrasonography of the carotid arteries, ECG, echocardiography with transesophageal studies to identify carotid and cardiac sources of emboli, and CT or MR studies for internal carotid artery dissection, if necessary.

Treatment

Retinal artery occlusions require urgent referral to an emergency department for imaging and clinical assessment to prevent subsequent stroke. If the patient is seen within a few hours after onset, emergency treatment, comprising laying the patient flat, ocular massage, high concentrations of inhaled oxygen, intravenous acetazolamide, and anterior chamber paracentesis, may influence the visual outcome. Early thrombolysis, particularly by local intra-arterial injection but also intravenously, has shown good results in central retinal artery occlusion not due to giant cell arteritis. However, local intra-arterial injection of thrombolytic agents has a high incidence of adverse effects and may be difficult to accomplish quickly enough after the occlusion develops to prevent permanent vision loss due to inner retinal ischemia, which non-human primate studies suggest occurs within 90 minutes of occlusion.

In giant cell arteritis, there is risk of involvement of the other eye without prompt treatment. Recommended initial empiric treatment is intravenous methylprednisolone 1 g/day for 3 days. Whether oral methylprednisolone is similarly effective is unknown. All patients require subsequent long-term corticosteroid therapy (eg, oral prednisone); concomitant administration of long-term low-dose aspirin therapy is controversial. Tocilizumab, a monoclonal antibody against the receptor for interleukin-6, is also approved to treat adults with giant cell arteritis. There must be close monitoring to ensure that symptoms resolve and do not recur. Temporal artery biopsy should be performed promptly to confirm the diagnosis (see Polymyalgia Rheumatica & Giant Cell Arteritis, Chapter 20).

Patients with embolic retinal artery occlusion with 70–99% ipsilateral carotid artery stenosis, and possibly those with 50–69% stenosis, should be considered for carotid endarterectomy or possibly angioplasty with stenting to be performed within 2 weeks (see Chapters 12 and 24). Retinal embolization due to cardiac disease such as atrial fibrillation or a hypercoagulable state usually requires anticoagulation. Cardiac valvular disease and patent foramen ovale may require surgical treatment.

When to Refer

- Patients with retinal artery occlusions should be referred immediately to an emergency department to evaluate for stroke manifestations.
- Patients with central retinal artery occlusion should be referred emergently to an ophthalmologist.
- Patients with branch retinal artery occlusion should be referred urgently.
- Patients with suspected giant cell arteritis should be referred to a rheumatologist to guide management.

When to Admit

Patients with visual loss due to giant cell arteritis may require emergency admission for high-dose corticosteroid therapy and close monitoring to ensure adequate treatment.

Biousse V et al. Management acute retinal ischemia: follow the guidelines! Ophthalmology. 2018;125:1597. [PMID: 29716787]

Fallico M et al. Risk of acute stroke in patients with retinal artery occlusion: a systematic review and meta-analysis. Eye (Lond). 2020;34:683. [PMID: 31527762]

Flaxel CJ et al. Retinal and ophthalmic artery occlusions Preferred Practice Pattern®. Ophthalmology. 2020;127:P259. [PMID: 31757501]

Serling-Boyd N et al. Recent advances in the diagnosis and management of giant cell arteritis. Curr Opin Rheumatol. 2020;32:201. [PMID: 32168069]

TRANSIENT MONOCULAR VISUAL LOSS

ESSENTIALS OF DIAGNOSIS

- Sudden-onset, monocular loss of vision usually lasting a few minutes with complete recovery.

Clinical Findings

A. Symptoms and Signs

Transient monocular visual loss ("ocular transient ischemic attack [TIA]") is usually caused by a retinal embolus from ipsilateral carotid disease or the heart. The visual loss is characteristically described as a curtain passing vertically across the visual field with complete monocular visual loss lasting a few minutes and a similar curtain effect as the episode passes (amaurosis fugax; also called "fleeting blindness"). An embolus is rarely seen on ophthalmoscopy. Other causes of transient, often recurrent, visual loss due to ocular ischemia are giant cell arteritis, hypercoagulable state (such as antiphospholipid syndrome), hyperviscosity, and severe occlusive carotid disease. More transient visual loss, lasting only a few seconds to 1 minute, usually recurrent, and affecting one or both eyes, occurs in patients with optic disk swelling, for example in those with raised intracranial pressure.

B. Diagnostic Studies

In most cases, clinical assessment and investigations are much the same as for retinal artery occlusion with emphasis on urgent neuroimaging to assess for cerebral infarction, as above, and identification of a source of emboli, since patients with embolic transient vision loss are at increased risk for stroke, MI, and other vascular events. Optic disk swelling requires different investigations (see Optic Disk Swelling, below).

Treatment

All patients with possible embolic transient visual loss should be treated immediately with oral aspirin (at least 81 mg daily), or another antiplatelet drug, until the cause has been determined. Affected patients with 70–99% (and possibly those with 50–69%) ipsilateral carotid artery stenosis

should be considered for urgent carotid endarterectomy or possibly angioplasty with stenting (see Chapters 12 and 24). In all patients, vascular risk factors (eg, hypertension) need to be controlled. Retinal embolization due to cardiac arrhythmia, such as atrial fibrillation, or a hypercoagulable state usually requires anticoagulation. Cardiac valvular disease and patent foramen ovale may require surgical treatment.

When to Refer

In all cases of episodic visual loss, early ophthalmologic consultation is advisable.

When to Admit

Referral to a stroke center or hospital admission is recommended in embolic transient visual loss if there have been two or more episodes in the preceding week ("crescendo TIA") or the underlying cause is cardiac or a hypercoagulable state.

Biousse V et al. Management of acute retinal ischemia: follow the guidelines! Ophthalmology. 2018;125:1597. [PMID: 29716787]
Sharma RA et al. New concepts on acute ocular ischemia. Curr Opin Neurol. 2019;32:19. [PMID: 30461463]

RETINAL DISORDERS ASSOCIATED WITH SYSTEMIC DISEASES

1. Diabetic Retinopathy

ESSENTIALS OF DIAGNOSIS

- Present in ~33% of all diagnosed diabetic patients.
- Present in ~20% of type 2 diabetic patients at time of diagnosis of diabetes.
- By 20 years after diagnosis of diabetes, 99% of type 1 diabetic patients and 60% of type 2 diabetic patients will have diabetic retinopathy.
- Nonproliferative diabetic retinopathy: can be mild, moderate, or severe. Microvascular changes are limited to the retina.
- Proliferative diabetic retinopathy: new blood vessels grow on the surface of the retina, optic nerve, or iris.
- Diabetic macular edema: central retinal swelling; can occur with any severity level of diabetic retinopathy; reduces visual acuity if the foveal center is involved.

General Considerations

Diabetic retinopathy is present in about one-third of patients in whom diabetes has been diagnosed, and about one-third of those have sight-threatening disease. In the United States, it affects about 4 million people; it is the leading cause of vision loss worldwide among adults aged 25–74 years; and the number of affected individuals aged 65 years or older is increasing. Worldwide, there are approximately 93 million people with diabetic retinopathy, including 28 million with vision-threatening disease. Retinopathy increases in prevalence and severity with increasing duration and poorer control of diabetes. In type 1 diabetes, retinopathy is not detectable for the first 5 years after diagnosis. In type 2 diabetes, about 20% of patients have retinopathy at diagnosis, likely because they had diabetes for a long time before diagnosis. Macular involvement is the most common cause of legal blindness in type 2 diabetes.

There are two main categories of diabetic retinopathy: nonproliferative and proliferative. Diabetic macular edema can occur at any stage. **Nonproliferative** (previously known as "background") **retinopathy** is subclassified as mild, moderate, or severe; **proliferative retinopathy** is less common but causes more severe visual loss.

Nonproliferative retinopathy represents the earliest stage of retinal involvement by diabetes. During this stage, the retinal capillaries leak proteins, lipids, or red cells into the retina. When this process occurs in the macula (clinically significant macular edema), visual acuity is affected; this is the most common cause of visual impairment in patients with type 2 diabetes.

Proliferative retinopathy involves the growth of new vessels and fibrous tissue on the surface of the retina, extending into the vitreous chamber. It is a consequence of capillary occlusion, which causes retinal ischemia and release of VEGF; this, in turn, stimulates new vessel growth.

Clinical Findings

Clinical assessment comprises visual acuity testing, stereoscopic examination of the retina, retinal imaging with optical coherence tomography, and sometimes fluorescein angiography.

Nonproliferative retinopathy manifests as microaneurysms, retinal hemorrhages, venous beading, retinal edema, and hard exudates. In mild nonproliferative diabetic retinopathy, there are mild retinal abnormalities without visual loss. Reduction of vision is most commonly due to diabetic macular edema, which may be focal or diffuse, but it can also be due to macular ischemia. Severe nonproliferative retinopathy is defined as having any one of the following: severe intraretinal hemorrhages and microaneurysms in four quadrants, venous beading in two or more quadrants, or intraretinal microvascular abnormalities in at least one quadrant.

Proliferative retinopathy is characterized by neovascularization, arising from either the optic disk or the retinal vascular arcades. Prior to proliferation of new capillaries, a preproliferative phase often occurs in which arteriolar ischemia is manifest as cotton-wool spots (small infarcted areas of retina). Vision is usually normal until macular edema, vitreous hemorrhage, or retinal detachment occurs. Proliferation into the vitreous of blood vessels, with associated fibrosis, may lead to vitreous hemorrhage (common) and tractional retinal detachment.

Diabetic retinopathy may worsen after bariatric surgery or in patients with long-standing hyperglycemia that is rapidly brought under tight control, such as after receiving an insulin pump with continuous glucose monitoring. It is believed that capillary endothelial cells retain "metabolic memory" of hyperglycemia and that epigenetic changes persist for several months after the hyperglycemia is corrected, sometimes causing retinopathy progression after intensive glycemic control is initiated; however, after the first 18–24 months, rates of progression are significantly lower in patients treated with intensive control compared to conventional regimens.

Screening

Visual symptoms and visual acuity are poor guides to the presence of diabetic retinopathy. Patients with diabetes mellitus should undergo regular fundus photography, which can be performed using telemedicine that may involve computer detection software programs, or dilated slit-lamp examination of the retina. Patients with type 1 diabetes mellitus should be screened 5 years after the diabetes is diagnosed. Patients with type 2 diabetes mellitus should be screened at or shortly after diagnosis of diabetes. More frequent monitoring is required in women with type 1 or 2 diabetes during pregnancy and in those planning pregnancy, and for the first 2 years after intensive glycemic control is initiated.

Treatment

Treatment includes optimizing blood glucose, blood pressure, kidney function, and serum lipids. When patients are initially brought into intensive glycemic control, they should be examined every 1–2 months so they can be treated if retinopathy progresses. Glycemic control is the most important modifiable factor in treating patients with diabetic retinopathy, but intensive blood pressure control and avoiding tobacco use also slow retinopathy progression.

Macular edema and exudates, but not macular ischemia, may respond to laser photocoagulation; to intravitreal administration of a VEGF inhibitor (ranibizumab, bevacizumab, aflibercept, or brolucizumab) or corticosteroid (triamcinolone, dexamethasone implant, or fluocinolone implant); or to vitrectomy. VEGF inhibitor therapy improves diabetic retinopathy severity in eyes at all levels of nonproliferative diabetic retinopathy and is the mainstay of treatment for diabetic macular edema.

In patients with **severe nonproliferative retinopathy,** fluorescein angiography can demonstrate the extent of retinal ischemia, which can help determine whether panretinal laser photocoagulation should be performed prophylactically. Vitrectomy is necessary to remove persistent vitreous hemorrhage, improve vision, allow panretinal laser photocoagulation, treat tractional retinal detachment involving the macula, and manage rapidly progressive proliferative disease.

Proliferative retinopathy is usually treated by intravitreal injection of a VEGF inhibitor or panretinal laser photocoagulation, preferably before vitreous hemorrhage or tractional detachment has occurred. Proliferative diabetic retinopathy, especially after successful laser treatment, is not a contraindication to treatment with thrombolytic agents, aspirin, or warfarin unless there has been recent intraocular hemorrhage.

When to Refer

- All diabetic patients with sudden loss of vision or retinal detachment should be referred emergently to an ophthalmologist.
- Proliferative retinopathy or macular involvement requires urgent referral to an ophthalmologist.
- Severe nonproliferative retinopathy or unexplained reduction of visual acuity requires early referral to an ophthalmologist.

Flaxel CJ et al. Diabetic Retinopathy Preferred Practice Pattern®. Ophthalmology. 2020;127:P66. [PMID: 31757498]

Gross JG et al; Diabetic Retinopathy Clinical Research Network. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA Ophthalmol. 2018;136:1138. [PMID: 30043039]

Hutton DW et al; DRCR Retina Network. Five-year cost-effectiveness of intravitreous ranibizumab therapy vs panretinal photocoagulation for treating proliferative diabetic retinopathy: a secondary analysis of a randomized clinical trial. JAMA Ophthalmol. 2019;137:1424. [PMID: 31647496]

Wong TY et al. Strategies to tackle the global burden of diabetic retinopathy: from epidemiology to artificial intelligence. Ophthalmologica. 2020;243:9. [PMID: 31408872]

2. Hypertensive Retinochoroidopathy

Systemic hypertension affects both the retinal and choroidal circulations. The clinical manifestations vary according to the degree and rapidity of rise in blood pressure and the underlying state of the ocular circulation (see Chapter 11). The most florid ocular changes occur in young patients with abrupt elevations of blood pressure, such as may occur in pheochromocytoma, malignant hypertension, or preeclampsia-eclampsia.

Chronic hypertension accelerates the development of atherosclerosis. The retinal arterioles become more tortuous and narrower and develop abnormal light reflexes ("silver-wiring" and "copper-wiring") (Figure 11–2). There is increased venous compression at the retinal arteriovenous crossings ("arteriovenous nicking"), predisposing to branch retinal vein occlusions. Flame-shaped hemorrhages occur in the nerve fiber layer of the retina. Detection is aided by nonmydriatic fundus photography.

Acute elevations of blood pressure result in loss of autoregulation in the retinal circulation, leading to breakdown of endothelial integrity and occlusion of precapillary arterioles and capillaries that manifest as cotton-wool spots, retinal hemorrhages, retinal edema, and retinal exudates, often in a stellate appearance at the macula. Vasoconstriction and ischemia in the choroid result in exudative retinal detachments and retinal pigment epithelial infarcts that later develop into pigmented lesions that may be focal,

linear, or wedge-shaped. The abnormalities in the choroidal circulation may also affect the optic nerve head, producing ischemic optic neuropathy with optic disk swelling. *Fundus abnormalities are the hallmark of hypertensive crisis with retinopathy (previously known as malignant hypertension) that requires emergency treatment* (see Chapter 11). Marked fundus abnormalities are likely to be associated with permanent retinal, choroidal, or optic nerve damage. Precipitous reduction of blood pressure may exacerbate such damage.

Chen X et al. Hypertensive retinopathy and the risk of stroke among hypertensive adults in China. Invest Ophthalmol Vis Sci. 2021;62:28. [PMID: 34283210]
Tsukikawa M et al. A review of hypertensive retinopathy and chorioretinopathy. Clin Optom (Auckl). 2020;12:67. [PMID: 32440245]

3. Blood Dyscrasias

Severe thrombocytopenia or anemia may result in various types of retinal or choroidal hemorrhages, including white-centered retinal hemorrhages (Roth spots) that occur in leukemia and other situations (eg, bacterial endocarditis). Involvement of the macula may result in permanent visual loss.

Sickle cell retinopathy is particularly common in hemoglobin SC disease but may also occur with other hemoglobin S variants. Manifestations include "salmon-patch" preretinal/intraretinal hemorrhages, "black sunbursts" resulting from intraretinal hemorrhage, and new vessels. Severe visual loss is rare with sickle cell retinopathy but more common in patients with pulmonary hypertension. Retinal laser photocoagulation reduces the frequency of vitreous hemorrhage from new vessels. Surgery is occasionally needed for persistent vitreous hemorrhage or tractional retinal detachment.

Alabduljalil T et al. Retinal ultra-wide-field colour imaging versus dilated fundus examination to screen for sickle cell retinopathy. Br J Ophthalmol. 2021;105:1121. [PMID: 32816790]
AlRyalat SA et al. Ocular manifestations of sickle cell disease in different genotypes. Ophthalmic Epidemiol. 2021;28:185. [PMID: 32757703]

4. HIV Infection/AIDS

See Chapter 31. **HIV retinopathy** causes cotton-wool spots, retinal hemorrhages, and microaneurysms but may also lead to reduced contrast sensitivity and retinal nerve fiber layer and outer retinal damage (HIV neuroretinal disorder).

CMV retinitis is less common since the availability of antiretroviral therapy (ART) but continues to be prevalent where resources are limited. It usually occurs when CD4 counts are below 50/mcL (0.05×10^9/L) and is characterized by progressively enlarging yellowish-white patches of retinal opacification and retinal hemorrhages, usually beginning adjacent to the major retinal vascular arcades. Patients are often asymptomatic until there is involvement of the fovea or optic nerve, or until retinal detachment develops. See Table 31–3 for initial therapeutic recommendations. Maintenance therapy can be achieved with lower-dose therapy or with intravitreal therapy. Systemic therapy has a greater risk of nonocular adverse effects but reduces mortality, incidence of nonocular CMV disease (but this is less common with ART), and incidence of retinitis in the other eye and avoids intraocular complications of intravitreal administration. In all patients with CMV retinitis, ART needs to be instituted or adjusted. This may lead to the immune reconstitution inflammatory syndrome (IRIS), which may lead to visual loss, predominantly due to cystoid macular edema. It may be possible to reduce the likelihood of IRIS by using immunomodulatory therapy to suppress the immune response causing the inflammation. If the CD4 count is maintained above 100/mcL (0.1×10^9/L), it may be possible to discontinue maintenance anti-CMV therapy.

Other ophthalmic manifestations of opportunistic infections occurring in AIDS patients include herpes simplex retinitis, which usually manifests as acute retinal necrosis; toxoplasmic and candidal chorioretinitis possibly progressing to endophthalmitis; herpes zoster ophthalmicus and herpes zoster retinitis, which can manifest as acute retinal necrosis or progressive outer retinal necrosis; and various entities due to syphilis, tuberculosis, or cryptococcosis. Kaposi sarcoma of the conjunctiva (see Chapter 31) and orbital lymphoma may also be seen on rare occasions.

Heiden D et al. Active cytomegalovirus retinitis after the start of antiretroviral therapy. Br J Ophthalmol. 2019;103:157. [PMID: 30196272]
Munro M et al. Cytomegalovirus retinitis in HIV and non-HIV individuals. Microorganisms. 2019;8:55. [PMID: 31905656]
Sudharshan S et al. Human immunodeficiency virus and intraocular inflammation in the era of highly active antiretroviral therapy—an update. Indian J Ophthalmol. 2020;68:1787. [PMID: 32823395]
Tang Y et al. Clinical features of cytomegalovirus retinitis in HIV infected patients. Front Cell Infect Microbiol. 2020;10:136. [PMID: 32318357]

ISCHEMIC OPTIC NEUROPATHY

ESSENTIALS OF DIAGNOSIS

- Sudden painless visual loss with signs of optic nerve dysfunction.
- Optic disk swelling in anterior ischemic optic neuropathy.

Anterior ischemic optic neuropathy—due to inadequate perfusion of the posterior ciliary arteries that supply the anterior portion of the optic nerve—produces sudden visual loss, usually with an altitudinal field defect and optic disk swelling. In older patients, it may be caused by giant cell arteritis (arteritic anterior ischemic optic neuropathy). The predominant factor predisposing to nonarteritic anterior ischemic optic neuropathy, which subsequently affects

the other eye in around 15% of cases, is a congenitally crowded optic disk, compromising optic disk circulation. Other predisposing factors are systemic hypertension, diabetes mellitus, hyperlipidemia, systemic vasculitis, inherited or acquired thrombophilia, interferon-alpha therapy, and obstructive sleep apnea; hypotension and anemia during dialysis may cause bilateral anterior ischemic optic neuropathy. An association with phosphodiesterase type 5 inhibitors is controversial.

Posterior ischemic optic neuropathy, involving the retrobulbar optic nerve and thus not causing any optic disk swelling, may occur with severe blood loss; nonocular surgery, particularly prolonged lumbar spine surgery in the prone position with increased orbital pressure; severe burns; or in association with dialysis, as a consequence of profound hypotension and anemia. In all such situations, there may be several contributory factors.

Treatment

Arteritic anterior ischemic optic neuropathy necessitates emergency high-dose systemic corticosteroid treatment to prevent visual loss in the other eye. (See Central & Branch Retinal Artery Occlusions, above, and Polymyalgia Rheumatica & Giant Cell Arteritis, Chapter 20.) It is uncertain whether systemic or intravitreal corticosteroid therapy influences the outcome in nonarteritic anterior ischemic optic neuropathy or whether oral low-dose aspirin (~81 mg daily) reduces the risk of involvement of the other eye. In ischemic optic neuropathy after nonocular surgery or dialysis, treatment of marked anemia by blood transfusion may be beneficial.

When to Refer

Patients with ischemic optic neuropathy should be referred urgently to an ophthalmologist.

When to Admit

Patients with ischemic optic neuropathy due to giant cell arteritis or other vasculitis may require emergency admission for high-dose corticosteroid therapy and close monitoring to ensure that treatment is adequate.

Arora S et al. Sildenafil in ophthalmology: an update. Surv Ophthalmol. 2022;67:463. [PMID: 34175342]
Augstburger E et al. Acute ischemic optic nerve disease: pathophysiology, clinical features and management. J Fr Ophtalmol. 2020;43:e41. [PMID: 31952875]

OPTIC NEURITIS

ESSENTIALS OF DIAGNOSIS

- Subacute, usually unilateral, visual loss.
- Pain exacerbated by eye movements.
- Optic disk is usually normal in acute stage but subsequently develops pallor.

General Considerations

Inflammatory optic neuropathy is strongly associated with demyelinating disease (typical optic neuritis), particularly multiple sclerosis, but it also occurs in acute disseminated encephalomyelitis; sarcoidosis; neuromyelitis optica spectrum disorder, which is characterized by serum antibodies to aquaporin-4; in association with serum antibodies to myelin oligodendrocyte glycoprotein; following viral infection (usually in children); in varicella zoster virus infection; in autoimmune disorders, particularly SLE and Sjögren syndrome; during treatment with biologics; and by spread of inflammation from the meninges, orbital tissues, or paranasal sinuses.

Clinical Findings

Optic neuritis in demyelinating disease is characterized by unilateral loss of vision developing over a few days. Visual acuity ranges from 20/30 (6/9) to no perception of light, with more severe visual loss being associated with low serum vitamin D. In almost all cases there is pain behind the eye, exacerbated by eye movements, central visual field loss, color vision loss, and a relative afferent pupillary defect. In about two-thirds of cases, the optic nerve is normal during the acute stage (retrobulbar optic neuritis). In the remainder, the optic disk is swollen (papillitis) with occasional flame-shaped peripapillary hemorrhages. Visual acuity usually improves within 2–3 weeks and returns to 20/40 (6/12) or better in 95% of previously unaffected eyes. Optic atrophy subsequently develops if there has been extensive optic nerve fiber damage. Any patient without a known diagnosis of multiple sclerosis in whom visual recovery does not occur, or if there is continuing deterioration of vision, or pain persisting after 2 weeks, should undergo MRI of the head and orbits to look for periventricular white matter demyelination or a lesion compressing the optic nerve.

Treatment

In acute demyelinating optic neuritis, intravenous methylprednisolone (1 g daily for 3 days followed by a tapering course of oral prednisolone) has been shown to accelerate visual recovery but not to improve final vision. However, in clinical practice, the oral taper is not often prescribed. Use in an individual patient is determined by the degree of visual loss, the state of the other eye, and the patient's visual requirements. Newer therapies include monoclonal antibodies against immune cells and cell-based therapies to deplete or modulate T and B cell responses.

Atypical optic neuritis due to sarcoidosis, neuromyelitis optica, herpes zoster, or SLE generally has a poorer prognosis, requires immediate and more prolonged corticosteroid therapy, may require plasma exchange, and may necessitate long-term immunosuppression.

Prognosis

Among patients with a first episode of clinically isolated optic neuritis, multiple sclerosis will develop in 50% within

15 years; however, the likelihood of developing multiple sclerosis ranges from 25% for patients without demyelinating lesions on brain MRI to 72% in patients with one or more demyelinating lesions. The major risk factors are female sex and multiple white matter lesions on brain MRI. Many disease-modifying drugs are available to reduce the risk of further neurologic episodes and disability, but each has adverse effects that in some instances are life-threatening. Retinal nerve fiber layer optical coherence tomography quantifies axonal damage that can be used to monitor disease progression.

When to Refer

All patients with optic neuritis should be referred urgently for ophthalmologic or neurologic assessment.

Derdelinckx J et al. Cells to the rescue: emerging cell-based treatment approaches for NMOSD and MOGAD. Int J Mol Sci. 2021;22:7925. [PMID: 34360690]
Graves JS. Optical coherence tomography in multiple sclerosis. Semin Neurol. 2019;39:711. [PMID: 31847042]

OPTIC DISK SWELLING

Optic disk swelling may result from any orbital or optic nerve lesion causing nerve compression, severe hypertensive retinochoroidopathy, or raised intracranial pressure, the last necessitating urgent imaging to exclude an intracranial mass, hemorrhage, infection, or cerebral venous sinus occlusion. Intraocular causes include central retinal vein occlusion, posterior uveitis, and posterior scleritis. Optic nerve lesions causing disk swelling include anterior ischemic optic neuropathy; optic neuritis; optic nerve sheath meningioma; and infiltration by sarcoidosis, leukemia, or lymphoma.

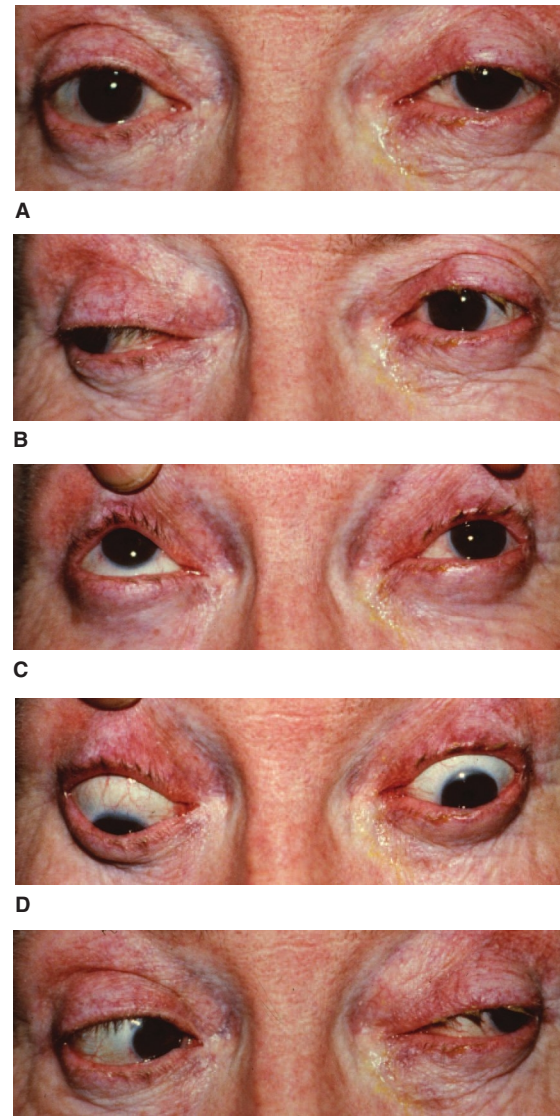
Papilledema (optic disk swelling due to raised intracranial pressure) is usually bilateral and most commonly produces enlargement of the blind spot without loss of acuity. Severe acute papilledema or chronic papilledema, as in idiopathic intracranial hypertension and cerebral venous sinus occlusion, may be associated with visual field and occasionally with profound visual acuity loss. All patients with chronic papilledema must be monitored carefully—especially their visual fields—and cerebrospinal fluid shunt or optic nerve sheath fenestration should be considered in those with progressive visual loss not controlled by medical therapy (weight loss where appropriate and usually acetazolamide in patients with idiopathic intracranial hypertension). In idiopathic intracranial hypertension, transverse venous sinus stenting is also an option.

Raoof N et al. Diagnosis and treatment of idiopathic intracranial hypertension. Cephalalgia. 2021;41:472. [PMID: 33631966]
Spiegel SJ et al. Neuro-ophthalmic emergencies. Neurol Clin. 2021;39:631. [PMID: 33896536]

CRANIAL NERVE PALSIES

A cranial nerve palsy of any of the three cranial nerves that supply the extraocular muscles can cause double vision.

In a complete **third nerve palsy,** there is ptosis with a divergent and slightly depressed eye (Figure 7–3). Extraocular movements are restricted in all directions except laterally (preserved lateral rectus function) (Figure 7–3E). Intact fourth nerve (superior oblique) function is detected by inward rotation on attempted depression of the eye. Pupillary involvement, manifesting as a relatively dilated pupil that does not constrict normally to light, usually



▲ **Figure 7–3.** Left partial third nerve palsy with ptosis **(A),** reduced adduction **(B),** reduced elevation **(C),** and reduced depression **(D)** but normal abduction **(E)** of the left eye.

means compression, which may be due to aneurysm of the posterior communicating artery or uncal herniation due to a supratentorial mass lesion. In acute painful isolated third nerve palsy with pupillary involvement, posterior communicating artery aneurysm must be excluded. Pituitary apoplexy is a rarer cause. Causes of isolated third nerve palsy without pupillary involvement include diabetes mellitus, hypertension, giant cell arteritis, and herpes zoster.

Fourth nerve palsy causes upward deviation of the eye with failure of depression on adduction. In acquired cases, there is vertical and torsional diplopia that is most apparent on looking down. Trauma is a major cause of acquired—particularly bilateral—fourth nerve palsy, but posterior fossa tumor and medical causes, such as in third nerve palsy, should also be considered. Similar clinical features are seen in congenital cases due to developmental anomaly of the nerve, muscle, or tendon.

Sixth nerve palsy causes convergent squint in the primary position with failure of abduction of the affected eye, producing horizontal diplopia that increases on gaze to the affected side and on looking into the distance. It is an important sign of raised intracranial pressure and may also be due to trauma, neoplasms, brainstem lesions, petrous apex lesions, or medical causes (such as diabetes mellitus, hypertension, giant cell arteritis, and herpes zoster).

In an isolated cranial nerve palsy presumed to be due a medical cause, brain MRI is not always required initially, but it is necessary if recovery has not begun within 3 months.

A cranial nerve palsy accompanied by other neurologic signs may be due to lesions in the brainstem, cavernous sinus, or orbit. Lesions around the cavernous sinus involve the first and second divisions of the trigeminal nerve, the third, fourth, and sixth cranial nerves, and occasionally the optic chiasm. Orbital apex lesions involve the optic nerve and the three cranial nerves supplying the extraocular muscles.

Myasthenia gravis and thyroid eye disease (see Graves Ophthalmopathy) should be considered in the differential diagnosis of disordered extraocular movements.

When to Refer

- In recent-onset isolated third nerve palsy, especially if there is pupillary involvement or pain, immediate referral is required for neurologic assessment and possibly CT, MRI, or catheter angiography for intracranial aneurysm.
- All patients with recent-onset double vision should be referred urgently to a neurologist or ophthalmologist, particularly if there are multiple cranial nerve dysfunctions or other neurologic abnormalities.

When to Admit

Patients with double vision due to giant cell arteritis may require emergency admission for high-dose corticosteroid therapy and close monitoring to ensure that treatment is adequate. (See Central & Branch Retinal Artery Occlusions and Chapter 20.)

Prasad S. A window to the brain: neuro-ophthalmology for the primary care practitioner. Am J Med. 2018;131:120. [PMID: 29079403]

THYROID EYE DISEASE (Graves Ophthalmopathy)

See Hyperthyroidism (Thyrotoxicosis) in Chapter 26.

ORBITAL CELLULITIS

Orbital cellulitis is characterized by fever, proptosis, restriction of extraocular movements, and swelling with redness of the lids. Immediate treatment with intravenous antibiotics is necessary to prevent optic nerve damage and spread of infection to the cavernous sinuses, meninges, and brain. Infection of the paranasal sinuses is the usual underlying cause. Infecting organisms include *S pneumoniae*, the incidence of which has been reduced by the administration of pneumococcal vaccine; other streptococci, such as the anginosus group; *H influenzae*; and, less commonly, *S aureus* including MRSA. Penicillinase-resistant penicillin, such as nafcillin, is recommended, possibly together with metronidazole or clindamycin to treat anaerobic infections. If trauma is the underlying cause, a cephalosporin, such as cefazolin or ceftriaxone, should be added to ensure coverage for *S aureus* and group A beta-hemolytic streptococci. If MRSA infection is a concern, vancomycin or clindamycin may be required. For patients with penicillin hypersensitivity, vancomycin, levofloxacin, and metronidazole are recommended. The response to antibiotics is usually excellent, but surgery may be required to drain the paranasal sinuses or orbital abscess. In immunocompromised patients, zygomycosis must be considered.

When to Refer

All patients with suspected orbital cellulitis must be referred emergently to an ophthalmologist.

Tsirouki T et al. Orbital cellulitis. Surv Ophthalmol. 2018;63:534. [PMID: 29248536]

OCULAR TRAUMA

Ocular trauma is an important cause of avoidable severe visual impairment at all ages, and it is the leading cause of monocular blindness in young adult men in the United States. Thorough but safe clinical assessment, supplemented when necessary by imaging, is crucial to effective management. Ocular damage and the possible need for early assessment by an ophthalmologist need to be borne in mind in the assessment of any patient with midfacial injury.

1. Conjunctival & Corneal Foreign Bodies

If a patient complains of "something in my eye" and gives a consistent history, a foreign body is usually present on the cornea or under the upper lid even though it may not be visible. Visual acuity should be tested before treatment is instituted to assess the severity of the injury and as a basis for comparison in the event of complications.

After a local anesthetic (eg, proparacaine, 0.5%) is instilled, the eye is examined with a slit lamp or with a hand flashlight, using oblique illumination, and loupe. The instillation of sterile fluorescein may make corneal foreign bodies more apparent, which are then removed with a sterile wet cotton-tipped applicator or hypodermic needle. Bacitracin-polymyxin ophthalmic ointment should be instilled. It is not necessary to patch the eye. All patients need to be advised to return promptly for reassessment if there is any increase in pain, redness, or impairment of vision.

Iron foreign bodies usually leave a diffuse rust ring. This requires excision and is best done under local anesthesia using a slit lamp. **Caution:** Anesthetic drops should not be given to the patient for self-administration.

If there is no infection, a layer of corneal epithelial cells will line the crater within 24 hours. While the epithelium is defective, the cornea is extremely susceptible to infection. Early infection is manifested by a white necrotic area around the crater and a small amount of gray exudate.

In the case of a foreign body under the upper lid, a local anesthetic is instilled and the lid is everted by grasping the lashes gently and exerting pressure on the mid portion of the outer surface of the upper lid with an applicator. If a foreign body is present, it can easily be removed by passing a wet sterile cotton-tipped applicator across the conjunctival surface.

When to Refer

Refer urgently to an ophthalmologist if a corneal foreign body cannot be removed or if there is suspicion of corneal infection.

Fraenkel A et al. Managing corneal foreign bodies in office-based general practice. Aust Fam Physician. 2017;46:89. [PMID: 28260265]

2. Intraocular Foreign Body

An intraocular foreign body requires emergency treatment by an ophthalmologist. Patients giving a history of "something hitting the eye"—particularly while hammering on metal or using grinding equipment—must be assessed for this possibility, especially when no corneal foreign body is seen, a corneal or scleral wound is apparent, or there is marked visual loss or media opacity. Such patients must be treated as for open globe injury and referred without delay. Intraocular foreign bodies significantly increase the risk of intraocular infection.

When to Refer

Patients with suspected intraocular foreign body must be referred emergently to an ophthalmologist.

Loporchio D et al. Intraocular foreign bodies: a review. Surv Ophthalmol. 2016;61:582. [PMID: 26994871]

3. Corneal Abrasions

A patient with a corneal abrasion complains of severe pain and photophobia. There is often a history of trauma to the eye, commonly involving a fingernail, piece of paper, or contact lens. Visual acuity is recorded, and the cornea and conjunctiva are examined with a light and loupe to rule out a foreign body. If an abrasion is suspected but cannot be seen, sterile fluorescein is instilled into the conjunctival sac: the area of corneal abrasion will stain because fluorescein stains areas that are devoid of epithelium.

Treatment includes bacitracin-polymyxin ophthalmic ointment or drops, or a fluoroquinolone topical antibiotic in contact lens wearers, as prophylaxis against infection. A mydriatic (cyclopentolate 1%) and either topical or oral NSAIDs can be used for pain control. Patching the eye is probably not helpful for small abrasions. Corneal abrasions heal more slowly in persons who smoke cigarettes. Recurrent corneal erosion may follow corneal abrasions.

Although treatment of pain from a corneal abrasion with topical tetracaine for 24 hours has been reported, there is a risk of delayed healing and severe corneal disease from misuse of topical anesthetics, so it is not recommended.

Wakai A et al. Topical non-steroidal anti-inflammatory drugs for analgesia in traumatic corneal abrasions. Cochrane Database Syst Rev. 2017;5:CD009781. [PMID: 28516471]

4. Contusions

Contusion injury of the eye (closed globe injury) and surrounding structures may cause ecchymosis ("black eye"), subconjunctival hemorrhage, edema of the cornea, hemorrhage into the anterior chamber (hyphema), rupture of the root of the iris (iridodialysis), paralysis of the pupillary sphincter, paralysis of the muscles of accommodation, cataract, dislocation of the lens, vitreous hemorrhage, retinal hemorrhage and edema (most common in the macular area), detachment of the retina, rupture of the choroid, fracture of the orbital floor ("blowout fracture"), or optic nerve injury. Many of these injuries are immediately obvious; others may not become apparent for days or weeks. The possibility of globe injury must always be considered in patients with facial injury, particularly if there is an orbital fracture. Patients with moderate to severe contusions should be seen by an ophthalmologist.

Any injury causing hyphema involves the danger of secondary hemorrhage, which may cause intractable

glaucoma with permanent visual loss. The patient should be advised to rest until complete resolution has occurred. Frequent ophthalmologic assessment is essential. Aspirin and any drugs inhibiting coagulation increase the risk of secondary hemorrhage and are to be avoided. Sickle cell anemia or trait adversely affects outcome.

When to Refer

Patients with moderate or severe ocular contusion should be referred to an ophthalmologist, emergently if there is hyphema.

5. Lacerations

A. Lids

If the lid margin is lacerated, the patient should be referred for specialized care, since permanent notching may result. Lacerations of the lower eyelid near the inner canthus often sever the lower canaliculus, for which canalicular intubation is likely to be required. Lid lacerations not involving the margin may be sutured like any skin laceration.

Ko AC et al. Eyelid and periorbital soft tissue trauma. Facial Plast Surg Clin North Am. 2017;25:605. [PMID: 28941512]

B. Conjunctiva

In lacerations of the conjunctiva, sutures are not necessary. To prevent infection, topical sulfonamide or other antibiotic is used until the laceration is healed.

C. Cornea or Sclera

Patients with suspected corneal or scleral laceration or rupture (open globe injury) must be seen emergently by an ophthalmologist. Manipulation is kept to a minimum, since pressure may result in extrusion of intraocular contents. The eye is bandaged lightly and covered with a shield that rests on the orbital bones above and below. The patient should be instructed not to squeeze the eye shut and to remain still. If there may be a metallic intraocular foreign body, a radiograph or CT scan is obtained to identify and localize it. *MRI is contraindicated because of the risk of movement of any metallic foreign body but may be useful for non-metallic foreign body.* Endophthalmitis occurs in over 5% of open globe injuries.

When to Refer

Patients with suspected open globe injury must be referred emergently to an ophthalmologist.

CHEMICAL CONJUNCTIVITIS & KERATITIS

Chemical burns are treated by copious irrigation of the eyes as soon as possible after exposure, with tap water, saline solution, or buffering solution if available. Neutralization of an acid with an alkali or vice versa may cause further damage. Alkali injuries are more serious and require prolonged irrigation, since alkalies are not precipitated by the proteins of the eye as are acids. It is important to remove any retained particulate matter, such as is typically present in injuries involving cement and building plaster. This often requires eversion of the upper lid. The pupil should be dilated with 1% cyclopentolate, 1 drop twice a day, to relieve discomfort, and prophylactic topical antibiotics should be started (Table 7–2). In moderate to severe injuries, intensive topical corticosteroids and topical and systemic vitamin C are also necessary. Complications include mucus deficiency, scarring of the cornea and conjunctiva, symblepharon (adhesions between the tarsal and bulbar conjunctiva), tear duct obstruction, and secondary infection. It is difficult to assess severity of chemical burns without slit-lamp examination.

Ahmmed AA et al. Epidemiology, economic and humanistic burdens of ocular surface chemical injury: a narrative review. Ocul Surf. 2021;20:199. [PMID: 33647471]
Sharma N et al. Treatment of acute ocular chemical burns. Surv Ophthalmol. 2018;63:214. [PMID: 28935121]

PRECAUTIONS IN MANAGEMENT OF OCULAR DISORDERS

1. Use of Local Anesthetics

Unsupervised self-administration of local anesthetics is dangerous because they are toxic to the corneal epithelium, delay healing, and the patient may further injure an anesthetized eye without knowing it.

Lee MD…Seitzman GD. Cornea specialists do not recommend routine usage of topical anesthetics for corneal abrasions. Ann Emerg Med. 2019;74:463. [PMID: 31445551]

2. Pupillary Dilation

Dilating the pupil can very occasionally precipitate acute glaucoma if the patient has a narrow anterior chamber angle and should be undertaken with caution if the anterior chamber is obviously shallow (readily determined by oblique illumination of the anterior segment of the eye). A short-acting mydriatic, such as tropicamide, should be used and the patient warned to report immediately if ocular discomfort or redness develops. Angle closure is more likely to occur if pilocarpine is used to overcome pupillary dilation than if the pupil is allowed to constrict naturally.

3. Corticosteroid Therapy

Comanagement with eye specialists is strongly recommended to monitor for ocular complications of corticosteroid therapy. Long-term use of local corticosteroids presents several hazards: ocular hypertension leading to open-angle glaucoma; cataract formation; and exacerbation of ocular infections, such as herpes simplex

(dendritic) and fungal keratitis. Furthermore, perforation of the cornea may occur when corticosteroids are used indiscriminately for infectious keratitis. The potential for causing or exacerbating systemic hypertension, diabetes mellitus, gastritis, osteoporosis, or glaucoma must always be borne in mind when systemic corticosteroids are prescribed for such conditions as uveitis or giant cell arteritis.

4. Contaminated Eye Medications

Ophthalmic solutions are prepared with the same degree of care as fluids intended for intravenous administration, but once bottles are opened there is always a risk of contamination, particularly with solutions of tetracaine, proparacaine, fluorescein, and any preservative-free preparations. Single-use fluorescein eyedrops or sterile fluorescein filter paper strips are recommended for use in place of multiple-use fluorescein solutions.

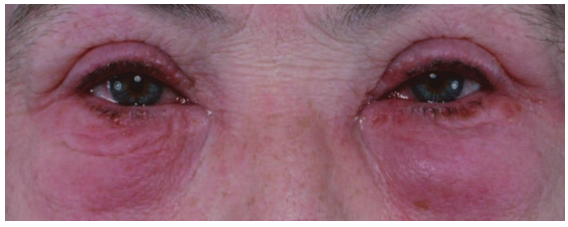
Whether in plastic or glass containers, eye solutions should not remain in use for long periods after the bottle is opened. Four weeks after opening is the usual maximum time for use of a solution containing preservatives before discarding. Preservative-free preparations should be kept refrigerated and usually discarded within 1 week after opening. Single-use products should not be reused.

If the eye has been injured by accident or by surgical trauma, it is of the greatest importance to use freshly opened bottles of sterile medications or single-use products.

5. Toxic & Hypersensitivity Reactions to Topical Therapy

In patients receiving long-term topical therapy, local toxic or hypersensitivity reactions to the active agent or preservatives may develop (Figure 7–4), especially if there is inadequate tear secretion. Preservatives in contact lens cleaning solutions may produce similar problems. Burning and soreness are exacerbated by drop instillation or contact lens insertion; occasionally, fibrosis and scarring of the conjunctiva and cornea may occur. Preservative-free topical medications and contact lens solutions are available.

An antibiotic instilled into the eye can sensitize the patient to that drug and cause an allergic reaction upon subsequent systemic administration. Potentially fatal anaphylaxis is known to occur in up to 0.3% of patients after intravenous fluorescein for fluorescein angiography. Anaphylaxis also has been reported after topical fluorescein.



▲ **Figure 7–4.** Periocular contact dermatitis due to eye drop preservative.

6. Systemic Effects of Ocular Drugs

The systemic absorption of certain topical drugs (through the conjunctival vessels and lacrimal drainage system) must be considered when there is a systemic medical contraindication to the use of the drug. Ophthalmic solutions of the nonselective beta-blockers, eg, timolol, may worsen bradycardia, heart failure, or asthma. Phenylephrine eye drops may precipitate hypertensive crises and angina. Adverse interactions between systemically administered and ocular drugs should also be considered. Using only 1 or 2 drops at a time and a few minutes of nasolacrimal occlusion or eyelid closure ensures maximum ocular efficacy and decreases systemic side effects of topical agents.

ADVERSE OCULAR EFFECTS OF SYSTEMIC DRUGS

Systemically administered drugs produce a wide variety of adverse effects on the visual system. Table 7–3 lists the major examples. The likelihood of most complications is rare, but if visual changes develop while a patient is being treated with these medications, the patient should be referred to an eye care professional for an eye examination. Screening for toxic retinopathy is recommended at baseline in patients receiving long-term chloroquine or hydroxychloroquine therapy. If no baseline abnormalities are present, screening should be repeated annually beginning after 5 years. More frequent screening is necessary in patients treated with doses greater than 5.0 mg/kg real weight/day of hydroxychloroquine or greater than 2.3 mg/kg/day of chloroquine, in patients with kidney disease or in those taking tamoxifen.

Pentosan polysulfate (used to treat interstitial cystitis) has been associated with progressive vision loss due to maculopathy. Patients who receive pentosan polysulfate should be monitored with annual eye examinations, including color fundus photography, fundus autofluorescence, and optical coherence tomography images; irreversible progressive vision loss can occur after maculopathy develops.

Patients receiving long-term systemic corticosteroids are at increased risk for several ocular complications, including glaucoma, cataract, and central serous retinopathy. They should be referred to an eye care professional for an eye examination at baseline before starting corticosteroids and at any time if reduced or blurry vision develops.

An ophthalmologist should be informed whether a patient is taking or has ever taken alpha-adrenoreceptor antagonists (such as tamsulosin) before cataract surgery because these medications increase the risk of intraoperative floppy iris syndrome, which can make cataract surgery more challenging.

The chemotherapeutic MEK inhibitors are associated with ocular complications including serous retinal detachment,

Table 7–3. Adverse ophthalmic effects of systemic drugs (selected list).

Medications	Possible Ophthalmic Side Effects
Ophthalmic medications	
Carbonic anhydrase inhibitors (eg, acetazolamide, methazolamide)	Nearsightedness, angle-closure glaucoma due to ciliary body swelling
Beta-blockers (eg, timolol, betaxolol, levobunolol, metipranolol)	Bradycardia, arrhythmias, syncope, hypotension, bronchoconstriction
Respiratory medications	
Anticholinergic bronchodilators (eg, ipratropium)	Angle-closure glaucoma due to mydriasis, blurring of vision due to cycloplegia, dry eyes
Sympathomimetic bronchodilators (eg, salbutamol) and decongestants (eg, ephedrine)	Angle-closure glaucoma due to mydriasis
Cardiovascular system medications	
Amiodarone	Corneal deposits (vortex keratopathy), optic neuropathy, thyroid eye disease
Amlodipine	Chemosis (conjunctival edema)
Anticoagulants	Conjunctival, retinal, and vitreous hemorrhage
Chlorthalidone	Angle-closure glaucoma due to ciliary body swelling
Digoxin	Disturbance of color vision, photopsia, optic neuropathy
Furosemide	Angle-closure glaucoma due to ciliary body swelling
Phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil)	Color vision changes, nonarteritic anterior ischemic optic neuropathy
Statins	Extraocular muscle palsy (myasthenic syndrome)
Thiazides (eg, indapamide)	Angle-closure glaucoma, nearsightedness, xanthopsia (yellow vision), band keratopathy due to hypercalcemia, macular edema
Gastrointestinal medications	
Anticholinergic agents	Angle-closure glaucoma due to mydriasis, blurring of vision due to cycloplegia, dry eyes
H_2-blockers	Retinal vascular occlusion, optic neuropathy, retrobulbar optic neuritis
Urinary tract medications	
Alpha-adrenoceptor-antagonists (eg, doxazosin, prazosin, tamsulosin, terazosin)	Intraoperative floppy iris syndrome
Phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil)	Color vision changes, nonarteritic anterior ischemic optic neuropathy
Pentosan polysulfate sodium	Maculopathy
Anticholinergic agents	Angle-closure glaucoma due to mydriasis, blurring of vision due to cycloplegia, dry eyes
Finasteride	Floppy iris syndrome during intraocular surgery
CNS medications	
Amphetamines	Widening of palpebral fissure, blurring of vision due to mydriasis, elevated intraocular pressure
Anticholinergic agents including preoperative medications	Angle-closure glaucoma due to mydriasis, blurring of vision due to cycloplegia, dry eyes
Aripiprazole	Nearsightedness
Diazepam	Nystagmus
Haloperidol	Capsular cataract
Lithium carbonate	Proptosis, oculogyric crisis, nystagmus
MAO inhibitors	Nystagmus, visual hallucinations, diplopia, myasthenia gravis

(*continued*)

Table 7–3. Adverse ophthalmic effects of systemic drugs (selected list). (continued)

Medications	Possible Ophthalmic Side Effects
Morphine/opioids	Miosis, visual hallucinations, diplopia, dry eye
Neostigmine	Nystagmus, miosis
Olanzapine	Angle-closure glaucoma due to mydriasis
Phenothiazines (eg, chlorpromazine)	Pigmentary deposits in conjunctiva, cornea, lens, and retina; oculogyric crisis Chlorpromazine causes floppy iris syndrome during intraocular surgery
Phenytoin	Nystagmus
Quetiapine	Floppy iris syndrome during intraocular surgery
Retigabine	Ocular pigmentation and retinopathy
Risperidone, paliperidone	Floppy iris syndrome during intraocular surgery
SSRIs (eg, paroxetine, sertraline)	Angle-closure glaucoma, ischemic optic neuropathy, cataract
SNRIs (eg, venlafaxine)	Angle-closure glaucoma, mydriasis, dry eye
Thioridazine	Corneal and lens deposits, retinopathy, oculogyric crisis
Topiramate	Angle-closure glaucoma due to ciliary body swelling, nearsightedness, macular folds, anterior uveitis, corneal edema
Tricyclic agents (eg, imipramine)	Angle-closure glaucoma due to mydriasis, blurring of vision due to cycloplegia, dry eye
Triptans (eg, sumatriptan, zolmitriptan)	Angle-closure glaucoma due to ciliary body swelling, nearsightedness
Vigabatrin	Visual field constriction, cone dystrophy
Zonisamide	Angle-closure glaucoma due to ciliary body swelling, nearsightedness
Obstetric drugs	
Sympathomimetic tocolytics	Angle-closure glaucoma due to mydriasis
Hormonal agents	
Aromatase inhibitors (eg, anastrozole)	Dry eye, vitreo-retinal traction, retinal hemorrhages
Cabergoline	Angle-closure glaucoma
Female sex hormones	Retinal artery occlusion, retinal vein occlusion, papilledema, cranial nerve palsies, ischemic optic neuropathy
Tamoxifen	Crystalline retinal and corneal deposits, altered color perception, cataract, optic neuropathy, macular edema, retinal pigmentary change
Immunomodulators	
Alpha-interferon	Retinopathy, keratoconjunctivitis, dry eyes, optic neuropathy
Corticosteroids	Cataract (posterior subcapsular); susceptibility to viral (herpes simplex), bacterial, and fungal infections; steroid-induced glaucoma; idiopathic intracranial hypertension; central serous retinopathy
NSAIDs	Corneal opacity, vortex keratopathy, periorbital edema, dry eye
Cyclosporine	Posterior reversible leukoencephalopathy
Fingolimod	Macular edema, retinal vein occlusion
Tacrolimus	Optic neuropathy, posterior reversible leukoencephalopathy
Antibiotics	
Chloramphenicol	Optic neuropathy
Clofazimine	Crystalline deposits (conjunctiva, cornea, iris)
Ethambutol	Optic neuropathy
Fluoroquinolones	Diplopia, retinal detachment
Isoniazid	Optic neuropathy
Linezolid	Optic neuropathy

(*continued*)

Table 7–3. Adverse ophthalmic effects of systemic drugs (selected list). (continued)

Medications	Possible Ophthalmic Side Effects
Rifabutin	Uveitis
Streptomycin	Optic neuropathy, epidermal necrolysis
Sulfonamides	Nearsightedness, angle-closure glaucoma due to ciliary body swelling
Tetracycline, doxycycline, minocycline	Papilledema
Antivirals	
Cidofovir	Uveitis
Antimalarial agents	
Chloroquine, hydroxychloroquine	Retinal degeneration principally involving the macula, vortex keratopathy
Quinine	Retinal toxicity, pupillary abnormalities
Amebicides	
Diiodohydroxyquinolone	Optic neuropathy
Chemotherapeutic agents	
Bortezomib	Chalazia
Chlorambucil	Optic neuropathy
Cisplatin	Optic neuropathy
Docetaxel	Lacrimal (canalicular) obstruction
Fluorouracil	Lacrimal (canalicular) obstruction
MEK inhibitors: trametinib, selumetinib, cobimetinib, pimasertib	Multifocal serous retinal detachment, retinal vein occlusion, cystoid macular edema
Vincristine	Optic neuropathy
Chelating agents	
Deferoxamine, deferasirox	Retinopathy, optic neuropathy, lens opacity
Penicillamine	Ocular pemphigoid, optic neuropathy, extraocular muscle palsy (myasthenic syndrome)
Oral hypoglycemic agents	
Chlorpropamide	Refractive error, epidermal necrolysis, optic neuropathy
Thiazolidinediones (glitazones)	Increase in diabetic macular edema
Vitamins	
Vitamin A	Papilledema
Vitamin D	Band-shaped keratopathy
Rheumatologic agents	
Chloroquine, hydroxychloroquine	Retinal degeneration principally involving the macula, vortex keratopathy
Gold salts	Deposits in the cornea, conjunctiva, and lens
NSAIDs (eg, ibuprofen, naproxen, indomethacin)	Vortex keratopathy (ibuprofen, naproxen), corneal deposits (indomethacin), retinal degeneration principally involving the macula (indomethacin)
Penicillamine	Ocular pemphigoid, optic neuropathy, extraocular muscle palsy (myasthenic syndrome)
Salicylates	Subconjunctival and retinal hemorrhages, nystagmus
Dermatologic agents	
Retinoids (eg, isotretinoin, tretinoin, acitretin, and etretinate)	Papilledema, blepharoconjunctivitis, corneal opacities, decreased contact lens tolerance, decreased dark adaptation, teratogenic ocular abnormalities, idiopathic intracranial hypertension, optic neuritis
Dupilumab	Conjunctivitis
Bisphosphonates	
Alendronate, pamidronate	Scleritis, episcleritis, uveitis

cystoid macular edema, and retinal vein occlusion. Patients receiving MEK inhibitors should have a complete eye examination at baseline before the initiation of these medications and should be referred for an eye examination if blurred or reduced vision develops while taking MEK inhibitors.

Arora S et al. Retinal toxicities of systemic anticancer drugs. Surv Ophthalmol. 2022;67:97. [PMID: 34048859]

Campbell RJ et al. Evolution in the risk of cataract surgical complications among patients exposed to tamsulosin: a population-based study. Ophthalmology. 2019;126:490. [PMID: 30648549]

Jain N et al; Macula Society Pentosan Polysulfate Maculopathy Study Group. Expanded clinical spectrum of pentosan polysulfate maculopathy: a Macula Society collaborative study. Ophthalmol Retina. 2022;6:219. [PMID: 34298229]

Syed MF et al. Ocular side effects of common systemic medications and systemic side effects of ocular medications. Med Clin North Am. 2021;105:425. [PMID: 33926639]

8 Otolaryngology Disorders

Elliott D. Kozin, MD
Lawrence R. Lustig, MD

DISEASES OF THE EAR

HEARING LOSS

ESSENTIALS OF DIAGNOSIS

- Hearing loss is generally categorized as either conductive or sensorineural.
- Hearing loss is most commonly due to cerumen impaction, transient eustachian tube dysfunction, or age-related hearing loss.

Classification & Epidemiology

Table 8–1 categorizes hearing loss as normal, mild, moderate, severe, or profound and outlines the vocal equivalent as well as the decibel range.

A. Conductive Hearing Loss

Conductive hearing loss results from a mechanical disruption of the external auditory canal or middle ear. Several mechanisms may result in impairment of the passage of sound vibrations to the inner ear, such as obstruction (eg, cerumen impaction), mass loading (eg, middle ear effusion), stiffness (eg, otosclerosis), and discontinuity (eg, ossicular disruption). Conductive losses in adults are most commonly due to cerumen impaction or transient eustachian tube dysfunction from upper respiratory tract infection. Persistent conductive losses usually result from chronic ear infection, trauma, or otosclerosis. Perforations of the tympanic membrane may also result in a conductive hearing loss. Conductive hearing loss is often correctable with medical (eg, use of a hearing aid) or surgical (eg, repair of tympanic membrane and ossicular chain) therapy, or both. CT of the temporal bone may be used as an adjunct to physical examination to determine the potential cause of conductive hearing loss.

B. Sensorineural Hearing Loss

Sensorineural hearing losses are common in adults and generally result from deficits of the inner ear or central (brain) auditory pathway. Sensory hearing loss results from deterioration of the cochlea, usually due to loss of sensory hair cells within the organ of Corti. The most common form of sensorineural hearing loss is **age-related hearing loss** that manifests as a gradually progressive, predominantly high-frequency hearing loss. Other causes of sensorineural hearing loss include excessive noise exposure; head trauma; ototoxic medications, such as cisplatin-based chemotherapy; and systemic diseases.

Sudden sensorineural hearing loss, often called idiopathic sudden sensorineural hearing loss, is considered an otologic emergency and may be treatable with oral or intratympanic corticosteroids if delivered within several weeks of onset. Long-term severe to profound sensorineural hearing loss due to deficits at the level of the inner ear may be correctable with surgery, such as cochlear implantation. Sensorineural hearing loss may also be due to deficits at the level of the central auditory pathway, including lesions involve the eighth cranial nerve, auditory nuclei, ascending tracts, or auditory cortex. Examples of central causes of hearing loss include acoustic neuroma, multiple sclerosis, and auditory neuropathy. Treatment of hearing loss due to central causes are usually aimed at addressing the underlying pathology.

Michels TC et al. Hearing loss in adults: differential diagnosis and treatment. Am Fam Physician. 2019;100:98. [PMID: 31305044]

US Preventive Services Task Force; Krist AH et al. Screening for hearing loss in older adults: US Preventive Services Task Force recommendation statement. JAMA. 2021;325:1196. [PMID: 33755083]

Evaluation of Hearing (Audiology)

In a quiet room, the hearing level may be estimated by having the patient repeat aloud words presented in a soft whisper, a normal spoken voice, or a shout. Normal spoken voice is about 60 decibels. A 512-Hz tuning fork is useful in differentiating conductive from sensorineural hearing loss. In the **Weber test,** the tuning fork is placed directly on the

Table 8–1. Hearing loss classification.

Classification	Vocal Equivalent	Decibel (dB) Range
Normal	Soft whisper	0–20 dB
Mild	Soft spoken voice	20–40 dB
Moderate	Normal spoken voice	40–60 dB
Severe	Loud spoken voice	60–80 dB
Profound	Shout	> 80 dB

forehead or front teeth. In conductive losses, the sound is heard as louder in the ear with *poorer hearing;* however, in sensorineural losses, the sound radiates to the ear that *hears better* than the other ear. In the **Rinne test,** the tuning fork is placed alternately on the mastoid bone (bone conduction) and in front of the ear canal (air conduction). In conductive losses greater than 25 dB, bone conduction sounds louder than air conduction.

Formal audiometric studies are performed in a soundproofed room. Pure-tone thresholds in decibels (dB) are obtained over the range of 250–8000 Hz. Conductive losses create a "gap" between the air and bone thresholds, whereas in sensorineural losses, both air and bone thresholds are equally diminished. Speech discrimination measures the clarity of hearing, reported as percentage correct (90–100% is normal). Auditory brainstem-evoked response screening method is most commonly used in newborn screening and may determine the approximate location of the lesion (eg, cochlea or brain). MRI scanning is the most sensitive and specific test to determine the possible location of a defect resulting in sensorineural hearing loss.

Every patient who complains of a hearing loss should be referred for audiologic evaluation unless the cause is easily remediable (eg, cerumen impaction, otitis media). Immediate audiometric referral is indicated for patients with idiopathic sudden sensorineural hearing loss because it requires treatment (corticosteroids) within a limited several-week time period.

Feltner C et al. Screening for hearing loss in older adults: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2021;325:1202. [PMID: 33755082]
Powell DS et al. Hearing impairment and cognition in an aging world. J Assoc Res Otolaryngol. 2021;22:387. [PMID: 34008037]
Sharma RK et al. Age-related hearing loss and the development of cognitive impairment and late-life depression: a scoping overview. Semin Hear. 2021;42:10. [PMID: 33883788]

Hearing Amplification

Patients with hearing loss not correctable by medical therapy may benefit from hearing amplification. Contemporary hearing aids are comparatively free of distortion and have been miniaturized to the point where they often may be contained entirely within the ear canal or lie inconspicuously behind the ear.

For patients with conductive loss or unilateral profound sensorineural loss, bone-conducting hearing aids directly stimulate the ipsilateral cochlea (for conductive losses) or contralateral ear (profound unilateral sensorineural loss). In most adults with severe to profound sensory hearing loss, the **cochlear implant**—an electronic device that is surgically implanted into the cochlea to stimulate the auditory nerve—offers socially beneficial auditory rehabilitation.

Buchman CA et al. Unilateral cochlear implants for severe, profound, or moderate sloping to profound bilateral sensorineural hearing loss: a systematic review and consensus statements. JAMA Otolaryngol Head Neck Surg. 2020;146:942. [PMID: 32857157]
Dixon PR et al. Health-related quality of life changes associated with hearing loss. JAMA Otolaryngol Head Neck Surg. 2020;146:630. [PMID: 32407468]

DISEASES OF THE AURICLE

Disorders of the auricle include skin cancers due to sun exposure. Traumatic auricular hematoma must be drained to prevent significant cosmetic deformity "cauliflower ear" or canal blockage resulting from dissolution of supporting cartilage. Similarly, cellulitis of the auricle must be treated promptly to prevent perichondritis and resultant deformity. **Relapsing polychondritis** is characterized by recurrent, frequently bilateral, painful episodes of auricular erythema and edema and sometimes progressive involvement of the cartilaginous tracheobronchial tree. Treatment with corticosteroids may help forestall cartilage dissolution. Polychondritis and perichondritis may be differentiated from cellulitis by sparing of involvement of the lobule, which does not contain cartilage.

Dalal PJ et al. Risk factors for auricular hematoma and recurrence after drainage. Laryngoscope. 2020;130:628. [PMID: 31621925]
Fousekis FS et al. Ear involvement in inflammatory bowel disease: A review of the literature. J Clin Med Res. 2018;10:609. [PMID: 29977417]

DISEASES OF THE EAR CANAL

1. Cerumen Impaction

Cerumen is a protective secretion produced by the outer portion of the ear canal. *In most persons, the ear canal is self-cleansing and no hygiene measures are recommended.* Cerumen impaction is most often self-induced through ill-advised cleansing attempts by entering the canal itself, eg, digital trauma or use of a cotton-tip applicator. It may be relieved by the patient using detergent ear drops (eg, 3% hydrogen peroxide; 6.5% carbamide peroxide) and irrigation, or by the clinician using mechanical removal, suction, or irrigation. Irrigation is performed with water at body temperature to avoid a vestibular caloric response. The stream should be directed at the posterior ear canal wall adjacent to the cerumen plug. Irrigation should be performed only when the tympanic membrane is known to be intact.

Use of jet irrigators (eg, WaterPik) should be avoided since they may result in tympanic membrane perforations. Following irrigation, the ear canal should be thoroughly dried (eg, by the patient using a hair blow-dryer on low-power setting or by the clinician instilling isopropyl alcohol) to reduce the likelihood of otitis externa. Specialty referral is indicated if impaction is frequently recurrent, if it has not responded to routine measures, or if there is tympanic membrane perforation or chronic otitis media.

Horton GA et al. Cerumen management: an updated clinical review and evidence-based approach for primary care physicians. J Prim Care Community Health. 2020;11: 2150132720904181. [PMID: 31994443]

2. Foreign Bodies

Foreign bodies in the ear canal are more frequent in children than in adults. Firm materials may be removed with a loop or a hook, taking care not to displace the object medially toward the tympanic membrane; microscopic guidance is helpful. Aqueous irrigation should not be performed for organic foreign bodies (eg, beans, insects), because water may cause them to swell. Living insects are best immobilized before removal by filling the ear canal with lidocaine or mineral oil. Lidocaine should *never* be used in a patient with a possible tympanic membrane perforation as this may result in a profound vestibular response.

Kim KH et al. Clinical characteristics of external auditory canal foreign bodies in children and adolescents. Ear Nose Throat J. 2020;99:648. [PMID: 31814447]

3. Otitis Externa

ESSENTIALS OF DIAGNOSIS

- Otalgia.
- Erythema, edema, and purulence of the external auditory canal skin.
- Diabetic or immunocompromised patients are at risk for "malignant" otitis externa (osteomyelitis of the skull base).

General Considerations

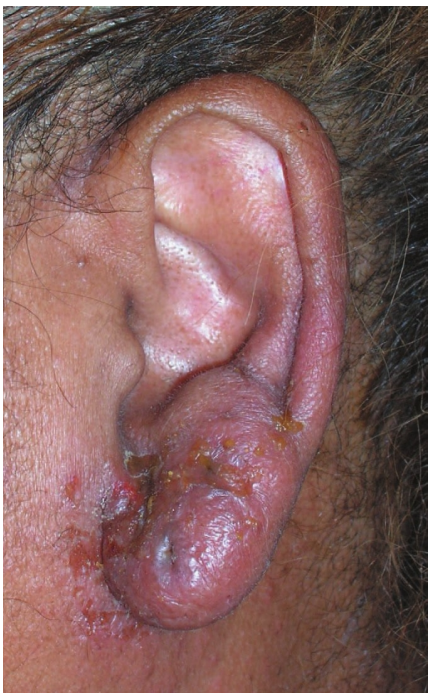
Otitis externa, often called "swimmer's ear," presents with otalgia with associated external auditory canal edema and purulent discharge. There is often a history of recent water exposure or mechanical trauma (eg, scratching, cotton applicators). Otitis externa is usually caused by gram-negative rods (eg, *Pseudomonas*, *Proteus*) or fungi (eg, *Aspergillus*), which grow in the presence of excessive moisture. In diabetic or immunocompromised patients, persistent otitis externa may evolve into osteomyelitis of the skull base (so-called **malignant otitis externa**). Usually caused by *Pseudomonas aeruginosa*, osteomyelitis begins in the floor of the ear canal and may extend into the middle fossa floor, the clivus, and even the contralateral skull base.

Clinical Findings

Examination reveals erythema and edema of the ear canal skin, often with a purulent exudate (Figure 8–1), as well as surrounding periauricular cellulitis. Manipulation of the auricle elicits pain. The lateral surface of the tympanic membrane is often erythematous. When the canal skin is very edematous, it may be impossible to visualize the tympanic membrane. In immunocompromised patients, such as those with diabetes, malignant otitis externa typically presents with persistent otorrhea; granulation tissue in the ear canal; deep otalgia; and in advanced cases, progressive palsies of cranial nerves, such as cranial nerve VI, VII, IX, X, XI, or XII. Diagnosis of malignant otitis externa is confirmed by the demonstration of osseous erosion on CT scanning and laboratory testing showing high inflammatory markers, such as ESR and CRP. MRI scanning is often important to rule out abscesses that may result from malignant otitis externa.

Treatment

Treatment of otitis externa involves protection of the ear from additional moisture and avoidance of further



▲ **Figure 8–1.** Malignant otitis externa in a 40-year-old woman with diabetes mellitus, with typical swelling and honey-colored crusting of the pinna. Both the external auditory canal and temporal bone were involved in the pseudomonal infection. (Used, with permission, from E.J. Mayeaux Jr, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine,* 2nd ed. McGraw-Hill, 2013.)

mechanical injury by scratching. In cases of moisture in the ear (eg, swimmer's ear), acidification with a drying agent (ie, a 50/50 mixture of isopropyl alcohol/white vinegar) is often helpful. When infected, an otic antibiotic solution or suspension of an aminoglycoside (eg, neomycin/polymyxin B) or fluoroquinolone (eg, ciprofloxacin), with or without a corticosteroid (eg, hydrocortisone), is usually effective. Purulent debris filling the ear canal should be gently removed to permit entry of the topical medication. Drops should be used abundantly (five or more drops three or four times a day) to penetrate the depths of the canal. When substantial edema of the canal wall prevents entry of drops into the ear canal, a wick is placed to facilitate their entry. In recalcitrant cases—particularly when cellulitis of the periauricular tissue has developed—oral fluoroquinolones (eg, ciprofloxacin, 500 mg twice daily for 1 week) are used because of their effectiveness against *Pseudomonas*. Newer medications that are ciprofloxacin suspensions may hold promise to improve otitis externa outcomes. Any case of persistent otitis externa in an immunocompromised or diabetic individual must be referred for specialty evaluation.

Treatment of malignant otitis externa requires prolonged antipseudomonal antibiotic administration, often for several months. Although intravenous therapy is often required initially (eg, ciprofloxacin 200–400 mg every 12 hours), selected patients may be graduated to oral ciprofloxacin (500–1000 mg twice daily). To avoid relapse, antibiotic therapy should be continued, even in the asymptomatic patient, until gallium scanning indicates marked reduction or resolution of the inflammation. Surgical debridement of infected bone is reserved for cases of deterioration despite medical therapy.

Smith ME et al; INTEGRATE (The UK ENT Trainee Research Network). Acute otitis externa: consensus definition, diagnostic criteria and core outcome set development. PLoS One. 2021;16:e0251395. [PMID: 33989313]

4. Pruritus

Pruritus of the external auditory canal, particularly at the meatus, is common. While it may be associated with otitis externa or with seborrheic dermatitis or psoriasis, most cases are self-induced from excoriation or overly zealous ear cleaning. To permit regeneration of the protective cerumen blanket, patients should be instructed to avoid use of soap and water or cotton swabs in the ear canal and avoid any scratching. Patients with excessively dry canal skin may benefit from application of mineral oil, which helps counteract dryness and repel moisture. When an inflammatory component is present, topical application of a corticosteroid (eg, 0.1% triamcinolone) may be beneficial.

5. Exostoses & Osteomas

Bony overgrowths of the ear canal are a frequent incidental finding and rarely have clinical significance. They present as skin-covered bony mounds in the medial ear canal obscuring the tympanic membrane to a variable degree. Solitary osteomas are of no significance as long as they do not cause obstruction or infection. Multiple exostoses, which are generally acquired from repeated exposure to cold water (eg, "surfer's ear"), may progress and require surgical removal if completely occluding the external auditory canal or resulting in frequent infections.

Simas V et al. Lifetime prevalence of exostoses in New Zealand surfers. J Prim Health Care. 2019;11:47. [PMID: 31039989]

6. Neoplasia

The most common neoplasm of the ear canal is squamous cell carcinoma. When an apparent otitis externa does not resolve on therapy, a malignancy should be suspected and biopsy performed. This disease carries a very high 5-year mortality rate because the tumor tends to invade the lymphatics of the cranial base and must be treated with wide surgical resection and radiation therapy. Adenomatous tumors, originating from the ceruminous glands, generally follow a more indolent course.

Komune N et al. Prognostic impact of tumor extension in patients with advanced temporal bone squamous cell carcinoma. Front Oncol. 2020;10:1229. [PMID: 32850367]
Piras G et al. Management of squamous cell carcinoma of the temporal bone: long-term results and factors influencing outcomes. Eur Arch Otorhinolaryngol. 2021;278:3193. [PMID: 32979119]
Seligman KL et al. Temporal bone carcinoma: treatment patterns and survival. Laryngoscope. 2020;130:E11. [PMID: 30874314]

DISEASES OF THE EUSTACHIAN TUBE

1. Eustachian Tube Dysfunction

ESSENTIALS OF DIAGNOSIS

- Aural fullness.
- Discomfort with barometric pressure change.
- Retracted eardrum.

The tube that connects the middle ear to the nasopharynx—the eustachian tube—provides ventilation and drainage for the middle ear. It is normally closed, opening only during swallowing or yawning. When eustachian tube function is compromised, air trapped within the middle ear becomes absorbed and negative pressure results. The most common causes of eustachian tube dysfunction are diseases associated with edema of the tubal lining, such as viral upper respiratory tract infections and seasonal allergies. The patient usually reports a sense of fullness in the ear and mild to moderate impairment of hearing. When the tube is only partially blocked, swallowing or yawning may elicit a popping or crackling sound. Examination may reveal retraction of the tympanic membrane and decreased mobility on pneumatic otoscopy. Following a viral illness,

this disorder is usually transient, lasting days to weeks. Treatment with systemic and intranasal decongestants (eg, pseudoephedrine, 60 mg orally every 4–6 hours; oxymetazoline, 0.05% spray every 8–12 hours), combined with **autoinsufflation** by forced exhalation against closed nostrils, may hasten relief. Autoinsufflation should not be recommended to patients with active intranasal infection, since this maneuver may precipitate middle ear infection. Allergic patients may also benefit from intranasal corticosteroids (eg, beclomethasone dipropionate, two sprays in each nostril twice daily for 2–6 weeks). Air travel, rapid altitudinal change, and underwater diving should be avoided until resolution.

An overly patent eustachian tube ("patulous eustachian tube") is a relatively uncommon, though quite distressing problem. Typical complaints include fullness in the ear and autophony (an exaggerated ability to hear oneself breathe and speak). A patulous eustachian tube may develop during rapid weight loss, such as following pregnancy, or it may be idiopathic. In contrast to eustachian tube dysfunction, the aural pressure is often made worse by exertion and may diminish during an upper respiratory tract infection. Although physical examination is usually normal, respiratory excursions of the tympanic membrane may occasionally be detected during vigorous breathing. Treatment includes avoidance of decongestant products and rarely surgery on the eustachian tube itself.

Froehlich MH et al. Eustachian tube balloon dilation: a systematic review and meta-analysis of treatment outcomes. Otolaryngol Head Neck Surg. 2020;163:870. [PMID: 32482125]
Tucci DL et al. Clinical consensus statement: balloon dilation of the eustachian tube. Otolaryngol Head Neck Surg. 2019;161:6. [PMID: 31161864]

2. Serous Otitis Media

ESSENTIALS OF DIAGNOSIS

- Eustachian tube obstruction is the underlying cause.
- Resultant negative pressure causes transudation of fluid into the middle ear and stasis.

Prolonged eustachian tube dysfunction with resultant negative middle ear pressure may cause a transudation of fluid. In adults, serous otitis media usually occurs with an upper respiratory tract infection, with barotrauma, or with chronic allergic rhinitis, but when persistent and unilateral, nasopharyngeal carcinoma must be excluded. The tympanic membrane is dull and hypomobile, occasionally accompanied by air bubbles in the middle ear and conductive hearing loss. The treatment of serous otitis media is similar to that for eustachian tube dysfunction. When medication fails to bring relief after several months, a ventilating tube placed through the tympanic membrane may restore hearing and alleviate the sense of aural fullness.

Vanneste P et al. Otitis media with effusion in children: pathophysiology, diagnosis, and treatment. A review. J Otol. 2019; 14:33. [PMID: 31223299]

3. Barotrauma

Persons with poor eustachian tube function (eg, congenital narrowness or acquired mucosal edema) may be unable to equalize the barometric stress exerted on the middle ear by air travel, rapid altitudinal change, or underwater diving. The problem is generally most acute during airplane descent, since the negative middle ear pressure tends to collapse and block the eustachian tube, causing pain. Several measures are useful to enhance eustachian tube function and avoid otic barotrauma. The patient should be advised to swallow, yawn, and autoinsufflate frequently during descent. Oral decongestants (eg, pseudoephedrine, 60–120 mg) should be taken several hours before anticipated arrival time so that they will be maximally effective during descent. Topical decongestants, such as 1% phenylephrine or oxymetazoline nasal spray, should be administered 1 hour before arrival.

For acute negative middle ear pressure that persists on the ground, treatment includes decongestants and attempts at autoinsufflation. Myringotomy provides immediate relief and is appropriate in the setting of severe otalgia and hearing loss.

Underwater diving may represent an even greater barometric stress to the ear than flying. Patients should be warned to avoid diving when they have an upper respiratory infection or episode of nasal allergy. During the descent phase of the dive, if inflation of the middle ear via the eustachian tube has not occurred, pain will develop within the first 15 feet; the dive must be aborted. In all cases, divers must descend slowly and equilibrate in stages to avoid the development of severely negative pressures in the tympanum that may result in hemorrhage (hemotympanum) or in perilymphatic fistula. In the latter, the oval or round window ruptures, resulting in sensory hearing loss and acute vertigo. During the ascent phase of a saturation dive, sensory hearing loss or vertigo may develop as the first (or only) symptom of decompression sickness. Immediate recompression will return intravascular gas bubbles to solution and restore the inner ear microcirculation.

Tympanic membrane perforation is an absolute contraindication to diving, as the patient will experience an unbalanced thermal stimulus to the semicircular canals and may experience vertigo, disorientation, and even emesis.

Millan SB et al. Prevention of middle ear barotrauma with oxymetazoline/fluticasone treatment. Undersea Hyperb Med. 2021; 48:149. [PMID: 33975404]
Scarpa A et al. Inner ear disorders in SCUBA divers: a review. J Int Adv Otol. 2021;17:260. [PMID: 34100753]

DISEASES OF THE MIDDLE EAR

1. Acute Otitis Media

ESSENTIALS OF DIAGNOSIS

- Otalgia.
- Purulent fluid of the middle ear.
- Erythema and hypomobility of tympanic membrane.

General Considerations

Acute otitis media is a bacterial infection of the mucosally lined, air-containing spaces of the middle ear. Purulent material may extend to pneumatized mastoid air cells and petrous apex of the lateral skull base. Acute otitis media is usually precipitated by a viral upper respiratory tract infection that causes eustachian tube obstruction. This results in accumulation of fluid and mucus, which becomes secondarily infected by bacteria. The most common pathogens are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Streptococcus pyogenes.*

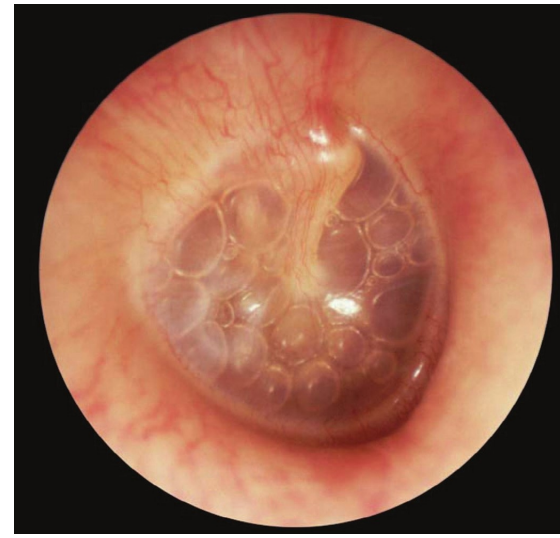
Clinical Findings

Acute otitis media may occur at any age. Presenting symptoms and signs include otalgia, aural pressure, decreased hearing, and often fever. The typical physical findings are erythema and decreased mobility of the tympanic membrane (Figure 8–2). Occasionally, bullae will appear on the tympanic membrane.

Rarely, when middle ear empyema is severe, the tympanic membrane bulges outward. In such cases, tympanic membrane rupture is imminent. Rupture is accompanied by a sudden decrease in pain, followed by the onset of otorrhea. With appropriate therapy, spontaneous healing of the tympanic membrane occurs in most cases. Acute mastoiditis results from an infection extending from the middle ear to the mastoid air cells. It is diagnosed by pain, postauricular erythema, and occasionally proptosis of the auricle. Frank swelling over the mastoid bone or the association of cranial neuropathies or central findings indicates severe disease requiring urgent care. Evaluation includes imaging, such as CT, to determine presence of "coalescence" of air cells and associated soft-tissue abscess.

Treatment

The treatment of acute otitis media is specific antibiotic therapy, often combined with nasal decongestants. The first-choice antibiotic is amoxicillin 1 g orally every 8 hours for 5–7 days. Alternatives (useful in resistant cases) are amoxicillin-clavulanate 875/125 mg or 2 g/125 mg ER every 12 hours for 5–10 days; or cefuroxime 500 mg or cefpodoxime 200 mg orally every 12 hours for 5–7 days. Recurrent acute otitis media may be managed with long-term antibiotic prophylaxis. Single daily oral doses of sulfamethoxazole (500 mg) or amoxicillin (250 or 500 mg) are given over a period of 1–3 months. Failure of this regimen to control infection is an indication for insertion of ventilating tubes.



▲ **Figure 8–2. Acute otitis media with effusion of right ear, with multiple air-fluid levels visible through a translucent, slightly retracted, nonerythematous tympanic membrane.** (Used, with permission, from Frank Miller, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Surgical drainage of the middle ear (myringotomy), debridement of the mastoid (mastoidectomy), or both are reserved for patients with severe otalgia or when complications of otitis (eg, mastoiditis, meningitis) have occurred.

Hoberman A et al. Tympanostomy tubes or medical management for recurrent acute otitis media. N Engl J Med. 2021; 384:1789. [PMID: 33979487]

Szmuilowicz J et al. Infections of the ear. Emerg Med Clin North Am. 2019;37:1. [PMID: 30454772]

2. Chronic Otitis Media

ESSENTIALS OF DIAGNOSIS

- Chronic otorrhea with or without otalgia.
- Tympanic membrane perforation with conductive hearing loss.
- Often amenable to surgical correction.

General Considerations

Chronic infection of the middle ear and mastoid generally develops as a consequence of recurrent acute otitis media,

although it may follow other diseases and trauma. Perforation or retraction of the tympanic membrane may be present. The bacteriology of chronic otitis media differs from that of acute otitis media. Common organisms include *P aeruginosa, Proteus* species, *Staphylococcus aureus,* and mixed anaerobic infections.

Clinical Findings

The clinical hallmark of chronic otitis media is purulent aural discharge. Drainage may be continuous or intermittent, with increased severity during upper respiratory tract infection or following water exposure. Pain is uncommon except during acute exacerbations. Conductive hearing loss results from destruction of the tympanic membrane or ossicular chain, or both.

Treatment

The medical treatment of chronic otitis media includes regular removal of infected debris, use of earplugs to protect against water exposure, and topical antibiotic drops (ofloxacin 0.3% or ciprofloxacin with dexamethasone) for exacerbations. Oral ciprofloxacin, active against *Pseudomonas*, 500 mg twice a day for 1–6 weeks, may help dry a chronically discharging ear.

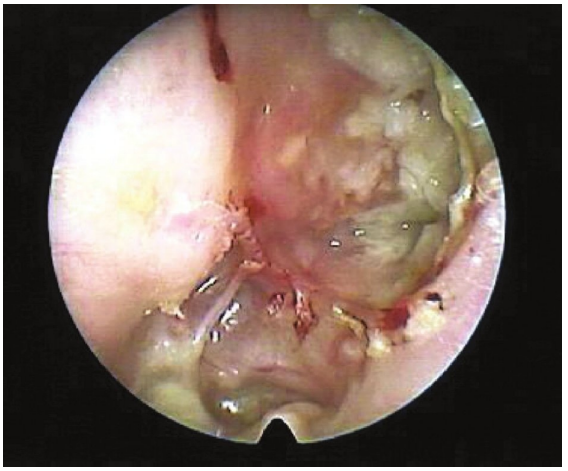
In most cases, surgery is the definitive management of tympanic membrane perforations with or without association of ossicular disruption. Successful reconstruction of the tympanic membrane may be achieved with autologous tissue, such as temporalis fascia, in about 90% of cases, often with improvement in conductive hearing.

Head K et al. Antibiotics versus topical antiseptics for chronic suppurative otitis media. Cochrane Database Syst Rev. 2020;1:CD013056. [PMID: 31902139]

Complications of Otitis Media

A. Cholesteatoma

Cholesteatoma is a special variety of chronic otitis media (Figure 8–3). The most common cause is prolonged eustachian tube dysfunction, with inward migration of the upper flaccid portion of the tympanic membrane. This creates a squamous epithelium-lined sac, which—when its neck becomes obstructed—may fill with desquamated keratin and become chronically infected. Cholesteatomas typically erode bone, including the ossicular chain with extension into the mastoid. Over time, cholesteatoma may erode into the inner ear, involve the facial nerve and, on rare occasions, spread intracranially. Otoscopic examination may reveal a retraction pocket of the tympanic membrane or a marginal tympanic membrane perforation that exudes keratin debris or granulation tissue. The treatment of cholesteatoma is surgical, including marsupialization of the sac or its complete removal. This may require the creation of a "mastoid bowl" in which the ear canal and mastoid are joined into a large common cavity that must be periodically cleaned.



▲ **Figure 8–3. Cholesteatoma.** (Used, with permission, from Vladimir Zlinsky, MD, in Roy F. Sullivan, PhD: Audiology Forum: Video Otoscopy, www.RCSullivan.com; from Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Basonbul RA et al. Systematic review of endoscopic ear surgery outcomes for pediatric cholesteatoma. Otol Neurotol. 2021; 42:108. [PMID: 33165162]

Luu K et al. Updates in pediatric cholesteatoma: minimizing intervention while maximizing outcomes. Otolaryngol Clin North Am. 2019;52:813. [PMID: 31280890]

B. Mastoiditis

Acute suppurative mastoiditis usually evolves following several weeks of inadequately treated acute otitis media. It is characterized by pain and postauricular cellulitis accompanied by a spiking fever. CT scan reveals coalescence of the mastoid air cells due to destruction of their bony septa. Initial treatment consists of intravenous antibiotics (eg, cefazolin 0.5–1.5 g every 6–8 hours) directed against the most common offending organisms (*S pneumoniae, H influenzae,* and *S pyogenes),* and myringotomy for culture and drainage. Failure of medical therapy indicates the need for surgical drainage, such as a mastoidectomy.

C. Petrous Apicitis

The medial portion of the petrous bone between the inner ear and clivus may become a site of persistent infection when the drainage of its pneumatic cell tracts becomes blocked. This may cause foul discharge, deep ear and retroorbital pain, and sixth nerve palsy (Gradenigo syndrome); meningitis may be a complication. Treatment is with prolonged antibiotic therapy (based on culture results) or surgical drainage via petrous apicectomy or both.

Isaac H et al. Transmastoid and transtemporal drainage of petrous apicitis with otitis media. Ann Otol Rhinol Laryngol. 2021;130:314. [PMID: 32772562]

D. Facial Paralysis

Facial palsy may be associated with either acute or chronic otitis media. In the acute setting, it results from inflammation of the seventh nerve in its middle ear segment. Treatment consists of myringotomy for drainage and culture, followed by intravenous antibiotics (based on culture results). The use of corticosteroids is controversial. The prognosis is excellent, with complete recovery in most cases.

Facial palsy associated with chronic otitis media usually evolves slowly due to chronic pressure on the seventh nerve in the middle ear or mastoid by cholesteatoma. Treatment requires surgical correction of the underlying disease. The prognosis is less favorable than for facial palsy associated with acute otitis media.

Mohan S et al. Considerations in management of acute otitis media in the COVID-19 era. Ann Otol Rhinol Laryngol. 2021;130:520. [PMID: 32911957]

E. Sigmoid Sinus Thrombosis

Trapped infection within the mastoid air cells adjacent to the sigmoid sinus may cause septic thrombophlebitis. This is heralded by signs of systemic sepsis (spiking fevers, chills), at times accompanied by signs of increased intracranial pressure (headache, lethargy, nausea and vomiting, papilledema). Diagnosis can be made noninvasively by magnetic resonance venography (MRV). Primary treatment is with intravenous antibiotics (based on culture results). Additional treatment, such as anticoagulation, surgical drainage, ligation of the internal jugular vein, or some combination thereof, may be indicated when embolization is suspected.

Ziv O et al. Post-operative clinical course in children undergoing mastoidectomy due to complicated acute mastoiditis. Eur Arch Otorhinolaryngol. 2021 Oct 29. [Epub ahead of print] [PMID: 34714371]

F. Central Nervous System Infection

Otogenic meningitis is the most common intracranial complication of ear infection. In the setting of acute suppurative otitis media, it arises from hematogenous spread of bacteria, most commonly *H influenzae* and *S pneumoniae*. In chronic otitis media, it results either from passage of infection along preformed pathways, such as the petrosquamous suture line, or from direct extension of disease through the dural plates of the petrous pyramid.

Epidural abscesses arise from direct extension of disease in the setting of chronic infection. They are usually asymptomatic but may present with deep local pain, headache, and low-grade fever. They are often discovered as an incidental finding at surgery. Brain abscess may arise in the temporal lobe or cerebellum as a result of septic thrombophlebitis adjacent to an epidural abscess. The predominant causative organisms are *S aureus, S pyogenes*, and *S pneumoniae*. Rupture into the subarachnoid space results in meningitis and often death. (See Chapter 30.)

Botti C et al. Pneumolabyrinth: a systematic review. Eur Arch Otorhinolaryngol. 2021;278:4619. [PMID: 33881577]

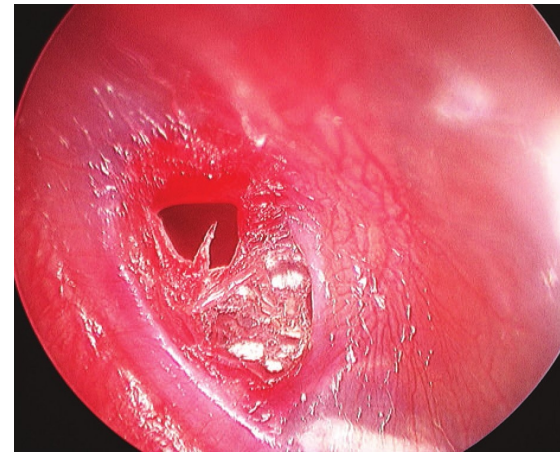
3. Otosclerosis

Otosclerosis is a progressive disease with a marked familial tendency that affects the bony otic capsule. Lesions involving the footplate of the stapes result in increased impedance to the passage of sound through the ossicular chain, producing conductive hearing loss. This may be treated either through the use of a hearing aid or surgical replacement of the stapes with a prosthesis (stapedectomy). When otosclerotic lesions involve the cochlea ("cochlear otosclerosis"), permanent sensory hearing loss may occur.

Gillard DM et al. Cost-effectiveness of stapedectomy vs hearing aids in the treatment of otosclerosis. JAMA Otolaryngol Head Neck Surg. 2020;146:42. [PMID: 31697352]
Yeh CF et al. Predictors of hearing outcomes after stapes surgery in otosclerosis. Acta Otolaryngol. 2019;139:1058. [PMID: 31617779]

4. Trauma to the Middle Ear

Tympanic membrane perforation may result from impact injury or explosive acoustic trauma (Figure 8–4). Spontaneous healing occurs in most cases. Persistent perforation may result from secondary infection brought on by exposure to water. During the healing period, patients should be advised to wear earplugs while swimming or bathing. Hemorrhage behind an intact tympanic membrane (hemotympanum) may follow blunt trauma or extreme barotrauma. Spontaneous resolution over several weeks is the usual course. When a conductive hearing loss greater than 30 dB persists for more than 3 months following trauma, disruption of the ossicular chain should be suspected. Middle ear exploration with reconstruction of the ossicular chain, combined with repair of the tympanic membrane when required, will usually restore hearing.



▲ **Figure 8–4. Traumatic perforation of the left tympanic membrane.** (Used, with permission, from William Clark, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Straughan AJ et al. Feel the burn! Fireworks-related otolaryngologic trauma. Ann Otol Rhinol Laryngol. 2021;130:1369. [PMID: 33834893]

5. Middle Ear Neoplasia

Primary middle ear tumors are rare. **Glomus tumors** arise either in the middle ear (glomus tympanicum) or in the jugular bulb with upward erosion into the hypotympanum (glomus jugulare). They present clinically with pulsatile tinnitus and hearing loss. A vascular mass may be visible behind an intact tympanic membrane. Large glomus jugulare tumors are often associated with multiple cranial neuropathies, especially involving nerves VII, IX, X, XI, and XII. Treatment usually requires surgery, radiotherapy, or both. **Pulsatile tinnitus thus warrants magnetic resonance angiography (MRA) and MRV to rule out a vascular mass.**

Yildiz E et al. Long-term outcome and comparison of treatment modalities of temporal bone paragangliomas. Cancers (Basel). 2021;13:5083. [PMID: 34680232]

EARACHE

Earache can be caused by a variety of otologic problems, but otitis externa and acute otitis media are the most common. Otitis externa and acute otitis media may be differentiated using history and physical examination, including pneumatic otoscopy. Pain out of proportion to the physical findings may be due to herpes zoster oticus, especially when vesicles appear in the ear canal or concha. Persistent pain and discharge from the ear suggest osteomyelitis of the skull base or cancer, and patients with these complaints should be referred for specialty evaluation.

Nonotologic causes of otalgia are numerous. The sensory innervation of the ear is derived from the trigeminal, facial, glossopharyngeal, vagal, and upper cervical nerves. Because of this rich innervation, referred otalgia is quite frequent. Temporomandibular joint dysfunction is a common cause of referred ear pain. Pain is exacerbated by chewing or psychogenic grinding of the teeth (bruxism) and may be associated with dental malocclusion. Repeated episodes of severe lancinating otalgia may occur in glossopharyngeal neuralgia. Infections and neoplasia that involve the oropharynx, hypopharynx, and larynx frequently cause otalgia. Persistent earache demands specialty referral to exclude cancer of the upper aerodigestive tract.

Norris CD et al. Secondary otalgia: referred pain pathways and pathologies. AJNR Am J Neuroradiol. 2020;41:2188. [PMID: 33093134]

DISEASES OF THE INNER EAR

1. Sensorineural Hearing Loss

Diseases of the cochlea and central auditory pathway result in hearing loss, a condition that is usually irreversible. The primary goals in the management of sensory hearing loss are prevention of further losses and functional improvement with auditory rehabilitation, such as with a hearing aid or cochlear implant.

A. Presbycusis

Presbycusis, or age-related hearing loss, is the most frequent cause of sensory hearing loss and is progressive, predominantly high-frequency, and symmetrical. Various etiologic factors (eg, prior noise trauma, drug exposure, genetic predisposition) may contribute to presbycusis. Most patients notice a loss of speech discrimination that is especially pronounced in noisy environments. About 25% of people between the ages of 65 and 75 years and almost 50% of those over 75 experience hearing difficulties. There is emerging evidence that conventional audiometry may not fully capture hearing loss (known as "hidden hearing loss"). Many patients may have subclinical hearing loss. New testing modalities are being devised to detect hearing loss in the setting of normal audiograms.

Choi JY et al. The impact of hearing loss on clinical dementia and preclinical cognitive impairment in later life. J Alzheimers Dis. 2021;81:963. [PMID: 33867361]
Drennan WR. Identifying subclinical hearing loss: extended audiometry and word recognition in noise. Audiol Neurootol. 2021 Nov 2. [Epub ahead of print] [PMID: 34727540]

B. Noise Trauma

Noise trauma is the second most common cause of sensorineural hearing loss. Sounds exceeding 85 dB for 8 hours or more are potentially injurious to the cochlea. The loss typically begins in the high frequencies (especially 4000 Hz) and, with continuing exposure, progresses to involve the speech frequencies. Among the more common sources of injurious noise are industrial machinery, weapons, and excessively loud music. Monitoring noise levels in the workplace by regulatory agencies has led to preventive programs that have reduced the frequency of occupational losses. Individuals of all ages, especially those with existing hearing losses, should wear earplugs when exposed to moderately loud noises and specially designed earmuffs when exposed to explosive noises.

Le Prell CG et al. Noise-induced hearing loss and its prevention: current issues in mammalian hearing. Curr Opin Physiol. 2020;18:32. [PMID: 32984667]
Neitzel RL et al. Risk of noise-induced hearing loss due to recreational sound: review and recommendations. J Acoust Soc Am. 2019;146:3911. [PMID: 31795675]

C. Physical Trauma

Concussive head trauma has effects on the inner ear similar to those of severe acoustic trauma. Some degree of sensory hearing loss may occur following concussion and is frequent after lateral skull base fracture.

Mizutari K. Update on treatment options for blast-induced hearing loss. Curr Opin Otolaryngol Head Neck Surg. 2019;27:376. [PMID: 31348022]

D. Ototoxicity

Ototoxic substances may affect both the auditory and vestibular systems. The most commonly used ototoxic medications are aminoglycosides; loop diuretics; and several antineoplastic agents, notably cisplatin. These medications may cause irreversible hearing loss even when administered in therapeutic doses. When using these medications, it is important to identify high-risk patients, such as those with preexisting hearing losses or kidney disease. Patients simultaneously receiving multiple ototoxic agents are at particular risk owing to ototoxic synergy. Useful measures to reduce the risk of ototoxic injury include serial audiometry, monitoring of serum peak and trough levels, and substitution of equivalent nonototoxic medications whenever possible.

It is possible for topical agents that enter the middle ear to be absorbed into the inner ear via the round window. When the tympanic membrane is perforated, use of potentially ototoxic ear drops (eg, neomycin, gentamicin) is best avoided.

Laurell G. Pharmacological intervention in the field of ototoxicity. HNO. 2019;67:434. [PMID: 30993373]
Rybak LP et al. Local drug delivery for prevention of hearing loss. Front Cell Neurosci. 2019;13:300. [PMID: 31338024]

E. Idiopathic Sudden Sensory Hearing Loss

Idiopathic sudden loss of hearing in one ear may occur at any age, but typically it occurs in persons over age 20 years. In the setting a normal otologic physical examination, symptoms may include hearing loss, aural fullness, tinnitus, and dizziness. The cause is unknown; however, idiopathic sudden hearing loss may result from a viral infection or a sudden vascular occlusion of the internal auditory artery. Obtaining an MRI is essential after the diagnosis to rule out retrocochlear pathology (eg, tumors); however, this should not delay treatment. Prompt treatment with corticosteroids has been shown to improve the odds of recovery. Intratympanic administration of corticosteroids alone or in association with oral corticosteroids has been associated with an equal or more favorable prognosis. Because treatment appears to be most effective as close to the onset of the loss as possible, and appears not to be effective after 6 weeks, a prompt audiogram should be obtained in all patients who present with sudden hearing loss without obvious middle ear pathology. Prognosis is mixed, with many patients suffering permanent deafness in the involved ear, while others have complete recovery.

Ahmadzai N et al. A systematic review and network meta-analysis of existing pharmacologic therapies in patients with idiopathic sudden sensorineural hearing loss. PLoS One. 2019;14:e0221713. [PMID: 31498809]
Chandrasekhar SS et al. Clinical practice guideline: sudden hearing loss (Update). Otolaryngol Head Neck Surg. 2019;161:S1. [PMID: 31369359]

F. Autoimmune Hearing Loss

Sensorineural hearing loss that occurs in both ears simultaneously may be associated with a wide array of systemic autoimmune disorders, such as SLE, granulomatosis with polyangiitis, and Cogan syndrome (hearing loss, keratitis, aortitis). The loss is most often progressive. The hearing level often fluctuates, with periods of deterioration alternating with partial or even complete remission. Usually, there is the gradual evolution of permanent hearing loss, which often stabilizes with some remaining auditory function but occasionally proceeds to complete deafness. Vestibular dysfunction, particularly dysequilibrium and postural instability, may accompany the auditory symptoms.

In many cases, the autoimmune pattern of audiovestibular dysfunction presents in the absence of recognized systemic autoimmune disease. Responsiveness to oral corticosteroid treatment is helpful in making the diagnosis and constitutes first-line therapy. If stabilization of hearing becomes dependent on long-term corticosteroid use, steroid-sparing immunosuppressive regimens may become necessary.

Yuen E et al. Hearing loss in patients with systemic lupus erythematosus: a systematic review and meta-analysis. Lupus. 2021;30:937. [PMID: 33645314]

2. Tinnitus

ESSENTIALS OF DIAGNOSIS

- Phantom noise or sounds.
- Persistent tinnitus often, though not always, indicates the presence of hearing loss.
- Intermittent periods of mild, high-pitched tinnitus lasting seconds to minutes are common in normal-hearing persons.

General Considerations

Tinnitus is defined as the sensation of sound in the absence of an exogenous sound source. Tinnitus can accompany any form of hearing loss, and its presence provides no diagnostic value in determining the cause of a hearing loss. Approximately 15% of the general population experiences some type of tinnitus, with prevalence beyond 20% in aging populations.

Clinical Findings

A. Symptoms and Signs

Though tinnitus is commonly associated with hearing loss, tinnitus severity correlates poorly with the degree of hearing loss. About one in seven tinnitus sufferers experiences severe annoyance, and 4% are severely disabled. When severe and persistent, tinnitus may interfere with sleep and ability to concentrate, resulting in considerable psychological distress.

Pulsatile tinnitus—often described by the patient as listening to one's own heartbeat—should be distinguished

from tonal tinnitus. Although often ascribed to conductive hearing loss, pulsatile tinnitus may be far more serious and may indicate a vascular abnormality, such as glomus tumor, venous sinus stenosis, carotid vaso-occlusive disease, arteriovenous malformation, or aneurysm.

A staccato "clicking" tinnitus may result from middle ear muscle spasm (middle ear myoclonus) or sometimes palatal myoclonus. The patient typically perceives a rapid series of popping noises, lasting seconds to a few minutes, accompanied by a fluttering feeling in the ear. Specialized forms of tympanometry may formally diagnose this condition, and it is typically treated surgically.

B. Diagnostic Testing

For routine, nonpulsatile tinnitus, audiometry should be ordered to rule out an associated hearing loss. For unilateral tinnitus, particularly associated with hearing loss in the absence of an obvious causative factor (ie, noise trauma), an MRI should be obtained to rule out a retrocochlear lesion, such as vestibular schwannoma. MRA and MRV and temporal bone CT should be considered for patients who have pulsatile tinnitus to exclude a causative vascular lesion or sigmoid sinus abnormality.

Treatment

The most important treatment of tinnitus is avoidance of exposure to excessive noise, ototoxic agents, and other factors that may cause cochlear damage. Masking the tinnitus with music or through amplification of normal sounds with a hearing aid may also bring some relief. In addition to masking techniques, habituation techniques, such as tinnitus retraining therapy and cognitive behavioral therapy, may prove beneficial in those with refractory symptoms. Among patients who have emotional distress due to tinnitus, numerous antidepressant and antipsychotic medications have been tried. Unfortunately, these medications do not treat the tinnitus directly but may allow the patient to cope with it better.

Conlon B et al. Bimodal neuromodulation combining sound and tongue stimulation reduces tinnitus symptoms in a large randomized clinical study. Sci Transl Med. 2020;12:eabb2830. [PMID: 33028707]

3. Hyperacusis

Excessive sensitivity to sound may occur following hearing loss, such as that due to noise trauma, in patients susceptible to migraines, or for psychological reasons. Patients with cochlear dysfunction commonly experience "recruitment," an abnormal sensitivity to loud sounds despite a reduced sensitivity to softer ones. Fitting hearing aids and other amplification devices to patients with recruitment requires use of compression circuitry to avoid uncomfortable overamplification.

Pienkowski M. Loud music and leisure noise is a common cause of chronic hearing loss, tinnitus and hyperacusis. Int J Environ Res Public Health. 2021;18:4236. [PMID: 33923580]

Ren J et al. Prevalence of hyperacusis in the general and special populations: a scoping review. Front Neurol. 2021;12:706555. [PMID: 34539554]

4. Vertigo

ESSENTIALS OF DIAGNOSIS

- Either a sensation of motion when there is no motion or an exaggerated sense of motion in response to movement.
- Duration of vertigo episodes with associated hearing loss or other neurologic issues are the keys to diagnosis.
- Evaluation includes audiogram, electronystagmography (ENG) or videonystagmography (VNG), and head MRI.

General Considerations

Vertigo can be caused by either a peripheral or central etiology, or both (Table 8–2).

Clinical Findings

A. Symptoms and Signs

Vertigo is the cardinal symptom of vestibular disease. Vertigo is typically experienced as a distinct "spinning" sensation or a sense of tumbling or of falling forward or backward. It should be distinguished from imbalance, light-headedness, and syncope, all of which are nonvestibular in origin (Table 8–3).

1. Peripheral vestibular disease—Peripheral vestibulopathy may cause vertigo of sudden onset, may be so severe that the patient is unable to walk or stand, and is frequently accompanied by nausea and vomiting. Tinnitus and hearing loss may be associated and provide strong support for a peripheral (ie, otologic) origin.

Critical elements of the history include the duration of the discrete vertiginous episodes (seconds, minutes to hours, or days), and associated symptoms (hearing loss). Triggers should be sought, including diet (eg, increased salt intake in the case of Ménière disease), stress, fatigue, and bright lights (eg, migraine-associated dizziness).

The physical examination of the patient with vertigo includes evaluation of the ears, observation of eye motion and nystagmus in response to head turning, cranial nerve examination, and Romberg testing. In acute peripheral lesions, nystagmus is usually horizontal with a rotatory component; the fast phase usually beats away from the diseased side. Visual fixation tends to inhibit nystagmus except in very acute peripheral lesions or with CNS disease. In benign paroxysmal positioning vertigo, **Dix-Hallpike testing** (quickly lowering the patient to the supine position with the head extending over the edge and placed 30 degrees lower than the body, turned either to the left or

Table 8–2. Causes of vertigo (listed in alphabetical order within categories).

Peripheral causes
Benign paroxysmal positioning vertigo
Ethanol intoxication
Inner ear barotraumas
Ménière disease
Semicircular canal dehiscence
Vestibular neuritis/labyrinthitis
Central causes
Cerebellar ataxia syndromes
Chiari malformation
Multiple sclerosis
Seizure
Wernicke encephalopathy
Mixed central and peripheral causes
Cerebellopontine angle tumors
Vestibular schwannoma
Meningioma
Endocrinopathies
Hypothyroidism
Pendred syndrome
Hyperviscosity syndromes
Waldenström macroglobulinemia
Infections
Lyme disease
Syphilis
Migraine
Stroke and vascular insufficiency
Anterior inferior cerebellar artery stroke
Posterior inferior cerebellar artery stroke
Vasculitides
Behçet disease
Cogan syndrome
Granulomatosis with polyangiitis
Susac syndrome
Vertebral artery insufficiency
Vascular compression

right) will elicit a delayed-onset (~10 seconds) fatigable nystagmus. Nonfatigable nystagmus in this position indicates CNS disease.

Since visual fixation often suppresses observed nystagmus, many of these maneuvers are performed with Frenzel goggles, which prevent visual fixation, and often bring out subtle forms of nystagmus. The **Fukuda test** can demonstrate vestibular asymmetry when the patient steps in place with eyes closed and consistently rotates in one direction.

Table 8–3. Common vestibular disorders: differential diagnosis based on classic presentations.

Duration of Typical Vertiginous Episodes	Auditory Symptoms Present	Auditory Symptoms Absent
Seconds	Perilymphatic fistula	Benign paroxysmal positioning vertigo (cupulolithiasis), vertebrobasilar insufficiency, migraine-associated vertigo
Hours	Ménière disease, syphilis	Migraine-associated vertigo
Days	Labyrinthitis, autoimmune inner ear disease, cerebellopontine angle tumor, ototoxicity	Vestibular neuronitis, migraine-associated vertigo, multiple sclerosis, cerebellar degeneration

2. Central disease—Vertigo arising from CNS disease (Table 8–2) tends to develop gradually and then becomes progressively more severe and debilitating. Nystagmus is not always present but can occur in any direction, may be dissociated in the two eyes, and is often non-fatigable, vertical rather than horizontal in orientation, without latency, and unsuppressed by visual fixation. ENG is useful in documenting these characteristics. Evaluation of audiovestibular dysfunction requires MRI of the brain.

Episodic vertigo can occur in patients with diplopia from external ophthalmoplegia and is maximal when the patient looks in the direction where the separation of images is greatest. Cerebral lesions involving the temporal cortex may also produce vertigo; it is sometimes the initial symptom of a seizure. Finally, vertigo may be a feature of a number of systemic disorders and can occur as a side effect of certain anticonvulsant, antibiotic, hypnotic, analgesic, and tranquilizer medications or of alcohol.

Welgampola MS et al. Dizziness demystified. Pract Neurol. 2019;19:492. [PMID: 31326945]

B. Vestibular Testing

Vestibular investigations, such as audiologic evaluation, caloric stimulation, electro- or videonystagmography (ENG or VNG), vestibular-evoked myogenic potentials (VEMPs), and MRI, are indicated in patients with persistent vertigo or when CNS disease is suspected. These studies help distinguish between central and peripheral lesions and identify causes requiring specific therapy. ENG consists of objective recording of the nystagmus induced by head and body movements, gaze, and caloric stimulation. It is helpful in quantifying the degree of vestibular hypofunction.

Zuniga SA et al. Efficient use of vestibular testing. Otolaryngol Clin North Am. 2021;54:875. [PMID: 34294436]

Vertigo Syndromes Due to Peripheral Lesions

A. Ménière Disease

The cause of Ménière disease is unknown. The classic syndrome consists of episodic vertigo, with discrete vertigo spells lasting 20 minutes to several hours in association with fluctuating, often low-frequency, sensorineural hearing loss, tinnitus (usually low-tone and "blowing" in quality), and a sensation of unilateral aural pressure (Table 8–3). These symptoms in presence of headaches or migraines may suggest migraine-associated dizziness. Primary treatment is aimed at decreasing dizzy episodes. There are no treatments for reduction in hearing loss. Treatment of Ménière disease typically involves preventive measures, including low-salt diet and daily diuretics (eg, acetazolamide). For symptomatic relief of acute vertigo attacks, lorazepam (0.5–1 mg) or diazepam (2–5 mg) can be used. Nausea may be treated with oral meclizine (25 mg). In refractory cases, patients may undergo intratympanic corticosteroid or gentamicin injections, endolymphatic sac decompression, or surgical or vestibular nerve section.

Gibson WPR. Meniere's disease. Adv Otorhinolaryngol. 2019; 82:77. [PMID: 30947172]

B. Labyrinthitis

Patients with labyrinthitis suffer from acute onset of continuous, usually severe vertigo lasting several days, accompanied by hearing loss and tinnitus. During a recovery period that lasts for several weeks, the vertigo gradually improves. Hearing may return to normal or remain permanently impaired in the involved ear. The cause of labyrinthitis is unknown. Treatment consists of antibiotics, if the patient is febrile or has symptoms of a bacterial infection, oral corticosteroids, and supportive care. Vestibular suppressants are useful during the acute phase of the attack (eg, diazepam) but should be discontinued as soon as feasible to avoid long-term dysequilibrium from inadequate compensation.

Welgampola MS et al. Dizziness demystified. Pract Neurol. 2019;19:492. [PMID: 31326945]

C. Benign Paroxysmal Positioning Vertigo

Patients suffering from recurrent spells of vertigo, lasting a few (10–15) seconds per spell, associated with changes in head position (often provoked by rolling over in bed), usually have benign paroxysmal positioning vertigo (BPPV). The term "positioning vertigo" is more accurate than "positional vertigo" because it is provoked by changes in head position rather than by the maintenance of a particular posture.

The typical symptoms of BPPV occur in clusters that persist for several days. There is a brief (10–15 seconds) latency period following a head movement before symptoms develop, and the acute vertigo subsides within 10–60 seconds, though the patient may remain imbalanced for several hours. Dizziness that lasts for more than a few seconds (that is several minutes or hours) is *not* BPPV. Constant repetition of the positional change leads to habituation. Since some CNS disorders can mimic BPPV (eg, vertebrobasilar insufficiency), recurrent cases warrant head MRI/MRA. In central lesions, there is no latent period, fatigability, or habituation of the symptoms and signs. Treatment of BPPV involves physical therapy protocols (eg, the **Epley maneuver** or **Brandt-Daroff exercises**), based on the theory that it results from cupulolithiasis (free-floating statoconia, also known as otoconia) within a semicircular canal.

Argaet EC et al. Benign positional vertigo, its diagnosis, treatment and mimics. Clin Neurophysiol Pract. 2019;4:97. [PMID: 31193795]
Instrum RS et al. Benign paroxysmal positional vertigo. Adv Otorhinolaryngol. 2019;82:67. [PMID: 30947198]

D. Vestibular Neuronitis

In vestibular neuronitis, a paroxysmal, usually single attack of vertigo occurs without accompanying impairment of auditory function and will persist for several days before gradually abating. During the acute phase, examination reveals nystagmus and absent responses to caloric stimulation on one or both sides. The cause of the disorder is unclear though presumed to be viral. Treatment consists of supportive care; vestibular suppressants, such as diazepam 2–5 mg every 6–12 hours during the acute phases of the vertigo only; oral corticosteroids may potentially be used; and antiemetics, such as ondansetron and meclizine, followed by vestibular therapy if the patient does not completely compensate.

Bronstein AM et al. Long-term clinical outcome in vestibular neuritis. Curr Opin Neurol. 2019;32:174. [PMID: 30566414]
Lee JY et al. Clinical characteristics of acute vestibular neuritis according to involvement site. Otol Neurotol. 2020;41:143. [PMID: 31789808]

E. Traumatic Vertigo

Labyrinthine concussion is the most common cause of vertigo following head injury. Symptoms generally diminish within several days but may linger for a month or more. Basilar skull fractures that traverse the inner ear usually result in severe vertigo lasting several days to a week and deafness in the involved ear. Chronic posttraumatic vertigo may result from cupulolithiasis. This occurs when traumatically detached statoconia (otoconia) settle on the ampulla of the posterior semicircular canal and cause an excessive degree of cupular deflection in response to head motion. Clinically, this presents as episodic positioning vertigo. Treatment consists of supportive care and vestibular suppressant medication (diazepam) during the acute phase of the attack and vestibular therapy.

Marcus HJ et al. Vestibular dysfunction in acute traumatic brain injury. J Neurol. 2019;266:2430. [PMID: 31201499]

F. Perilymphatic Fistula

Leakage of perilymphatic fluid from the inner ear into the tympanic cavity via the round or oval window is a very rare

cause of vertigo and sensory hearing loss. Most cases result from physical injury (eg, blunt head trauma, hand slap to ear); extreme barotrauma during airflight, scuba diving, etc; or vigorous Valsalva maneuvers (eg, during weight lifting). Treatment may require middle ear exploration and window sealing with a tissue graft.

Sarna B et al. Perilymphatic fistula: a review of classification, etiology, diagnosis, and treatment. Front Neurol. 2020;11:1046. [PMID: 33041986]

G. Cervicogenic Vertigo

Position receptors located in the facets of the cervical spine are important physiologically in the coordination of head and eye movements. Cervical proprioceptive dysfunction is a common cause of vertigo triggered by neck movements. This disturbance often commences after neck injury, particularly hyperextension; it is also associated with degenerative cervical spine disease. Although symptoms vary, vertigo may be triggered by assuming a particular head position as opposed to moving to a new head position (the latter typical of labyrinthine dysfunction). Cervical vertigo may often be confused with migraine-associated vertigo, which is also associated with head movement. Management consists of neck movement exercises to the extent permitted by orthopedic considerations.

Cherchi M et al. The enduring controversy of cervicogenic vertigo, and its place among positional vertigo syndromes. Audiol Res. 2021;11:491. [PMID: 34698085]
Ranalli P. An overview of central vertigo disorders. Adv Otorhinolaryngol. 2019;82:127. [PMID: 30947212]

H. Migrainous Vertigo

Episodic vertigo is frequently associated with migraine headache. Head trauma may also be a precipitating feature. The vertigo may be temporally related to the headache and last up to several hours, or it may also occur in the absence of any headache. Migrainous vertigo may resemble Ménière disease but without associated hearing loss or tinnitus. Accompanying symptoms may include head pressure; visual, motion, or auditory sensitivity and photosensitivity. Symptoms typically worsen with lack of sleep and anxiety or stress. Food triggers include caffeine, chocolate, and alcohol, among others. There is often a history of motion intolerance (easily carsick as a child). Migrainous vertigo may be familial. Treatment includes dietary and lifestyle changes (improved sleep pattern, avoidance of stress) and antimigraine prophylactic medication.

Hain T et al. Migraine associated vertigo. Adv Otorhinolaryngol. 2019;82:119. [PMID: 30947176]

I. Superior Semicircular Canal Dehiscence

Deficiency in the bony covering of the superior semicircular canal may be associated with vertigo triggered by loud noise exposure, straining, and an apparent conductive hearing loss. Autophony is also a common feature. Diagnosis is with coronal high-resolution CT scan and VEMP testing. Surgically resurfacing or plugging the dehiscent canal can improve symptoms.

Eberhard KE et al. Current trends, controversies, and future directions in the evaluation and management of superior canal dehiscence syndrome. Front Neurol. 2021;12:638574. [PMID: 33889125]

Vertigo Syndromes Due to Central Lesions

CNS causes of vertigo include brainstem vascular disease, arteriovenous malformations, tumors of the brainstem and cerebellum, multiple sclerosis, and vertebrobasilar migraine (Table 8–2). Vertigo of central origin often becomes unremitting and disabling. The associated nystagmus is often nonfatigable, vertical rather than horizontal in orientation, without latency, and unsuppressed by visual fixation. ENG is useful in documenting these characteristics. There are commonly other signs of brainstem dysfunction (eg, cranial nerve palsies; motor, sensory, or cerebellar deficits in the limbs) or of increased intracranial pressure. Auditory function is generally spared. The underlying cause should be treated.

Chari DA et al. The efficient dizziness history and exam. Otolaryngol Clin North Am. 2021;54:863. [PMID: 34294439]
Ranalli P. An overview of central vertigo disorders. Adv Otorhinolaryngol. 2019;82:127. [PMID: 30947212]

DISEASES OF THE CENTRAL AUDITORY & VESTIBULAR SYSTEMS

Lesions of the eighth cranial nerve and central audiovestibular pathways may produce hearing loss and dizziness (Table 8–3). One characteristic of neural hearing loss is deterioration of speech discrimination out of proportion to the decrease in pure tone thresholds. Another is auditory adaptation, wherein a steady tone appears to the listener to decay and eventually disappear. Auditory evoked responses are useful in distinguishing cochlear from neural losses and may give insight into the site of lesion within the central pathways.

The evaluation of central audiovestibular disorders usually requires imaging of the internal auditory canal, cerebellopontine angle, and brain with enhanced MRI.

1. Vestibular Schwannoma (Acoustic Neuroma)

Eighth cranial nerve schwannomas are among the most common intracranial tumors. Most are unilateral, but about 5% are associated with the hereditary syndrome neurofibromatosis type 2, in which bilateral eighth nerve tumors may be accompanied by meningiomas and other intracranial and spinal tumors. These benign lesions arise within the internal auditory canal and gradually grow to involve the cerebellopontine angle, eventually compressing the pons and resulting in hydrocephalus. Their typical auditory symptoms are unilateral hearing loss with a deterioration of speech discrimination exceeding that predicted by the degree of pure tone loss. Nonclassic presentations, such as sudden unilateral hearing loss, are fairly common. **Any individual with a unilateral**

or asymmetric sensorineural hearing loss should be evaluated for an intracranial mass lesion. Vestibular dysfunction more often takes the form of continuous dysequilibrium than episodic vertigo. Diagnosis is made by enhanced MRI. Treatment consists of observation, microsurgical excision, or stereotactic radiotherapy, depending on such factors as patient age, underlying health, and size of the tumor.

Kalogeridi MA et al. Stereotactic radiosurgery and radiotherapy for acoustic neuromas. Neurosurg Rev. 2020;43:941. [PMID: 30982152]
Leon J et al. Observation or stereotactic radiosurgery for newly diagnosed vestibular schwannomas: a systematic review and meta-analysis. J Radiosurg SBRT. 2019;6:91. [PMID: 31641546]

2. Vascular Compromise

Vertebrobasilar insufficiency is a common cause of vertigo in the elderly. It is often triggered by changes in posture or extension of the neck. Reduced flow in the vertebrobasilar system may be demonstrated noninvasively through MRA. Empiric treatment is with vasodilators and aspirin.

Cornelius JF et al. Compression syndromes of the vertebral artery at the craniocervical junction. Acta Neurochir Suppl. 2019;125:151. [PMID: 30610316]

3. Multiple Sclerosis

Patients with multiple sclerosis may suffer from episodic vertigo and chronic imbalance. Hearing loss in this disease is most commonly unilateral and of rapid onset. Spontaneous recovery may occur.

Kattah JC et al. Eye movements in demyelinating, autoimmune and metabolic disorders. Curr Opin Neurol. 2020;33:111. [PMID: 31770124]

OTOLOGIC MANIFESTATIONS OF AIDS

AIDS may result in many otologic signs and symptoms. The pinna and external auditory canal may be affected by Kaposi sarcoma and by persistent and potentially invasive fungal infections (particularly *Aspergillus fumigatus*). Serous otitis media due to eustachian tube dysfunction may arise from adenoidal hypertrophy (HIV lymphadenopathy), recurrent mucosal viral infections, or an obstructing nasopharyngeal tumor (eg, lymphoma). Unfortunately, ventilating tubes are seldom helpful and may trigger profuse watery otorrhea. Acute otitis media is usually caused by typical bacterial organisms, including *Proteus, Staphylococcus,* and *Pseudomonas,* and rarely, by *Pneumocystis jirovecii.* Sensorineural hearing loss is common and, in some cases, results from viral CNS infection. In cases of progressive hearing loss, cryptococcal meningitis and syphilis must be excluded. Acute facial paralysis due to herpes zoster infection (**Ramsay Hunt syndrome**) occurs commonly and follows a clinical course similar to that in nonimmunocompromised patients. Treatment is with high-dose acyclovir (see Chapter 32). Corticosteroids may also be effective as an adjunct.

Dawood G et al. Nature and extent of hearing loss in HIV-infected children: a scoping review. Int J Pediatr Otorhinolaryngol. 2020;134:110036. [PMID: 32335463]
Iacovou E et al. Diagnosis and treatment of HIV-associated manifestations in otolaryngology. Infect Dis Rep. 2012;4:e9. [PMID: 24470939]

DISEASES OF THE NOSE & PARANASAL SINUSES

INFECTIONS OF THE NOSE & PARANASAL SINUSES

Rhinosinusitis may be classified by duration of symptoms. Rhinosinusitis is called acute rhinosinusitis if less than 4 weeks' duration or as chronic rhinosinusitis if lasting more than 12 weeks, with or without acute exacerbations. Acute rhinosinusitis may also be classified by presumed etiology, such as viral rhinosinusitis or acute bacterial rhinosinusitis.

1. Viral Rhinosinusitis (Common Cold)

ESSENTIALS OF DIAGNOSIS

- Associated malaise, headache, and cough.
- Nasal congestion, facial pressure, rhinorrhea, and hyposmia.
- Erythematous, engorged nasal mucosa without intranasal purulence.
- Symptoms are self-limited, lasting typically < 10 days.

Clinical Findings

Due to the numerous serologic types of rhinoviruses, adenoviruses, and other viruses, patients remain susceptible to the common cold throughout life. These infections, while generally quite benign and self-limited, have been implicated in the development or exacerbation of more serious conditions, such as acute bacterial sinusitis and acute otitis media, asthma, cystic fibrosis, and bronchitis. Nasal congestion, decreased sense of smell, rhinorrhea, and sneezing accompanied by general malaise, throat discomfort and, occasionally, headache, are typical in viral infections. Nasal examination usually shows erythematous, edematous mucosa and a watery discharge. The presence of purulent nasal discharge suggests bacterial rhinosinusitis.

Najafloo R et al. Mechanism of anosmia caused by symptoms of COVID-19 and emerging treatments. ACS Chem Neurosci. 2021;12:3795. [PMID: 34609841]
Vance H et al. Addressing post-COVID symptoms: a guide for primary care physicians. J Am Board Fam Med. 2021;34:1229. [PMID: 34772779]

Treatment

The main treatment for viral rhinitis is supportive care, including rest, hydration, and use of over-the-counter analgesics and decongestants. There are no effective antiviral therapies for either the prevention or treatment of most viral rhinitis despite a common *misperception* among patients that antibiotics are helpful. Buffered hypertonic saline (3–5%) nasal irrigation has been shown to improve symptoms and reduce the need for NSAIDs. Other supportive measures, such as oral decongestants (pseudoephedrine, 30–60 mg every 4–6 hours or 120 mg twice daily), may provide some relief of rhinorrhea and nasal obstruction.

Nasal sprays, such as oxymetazoline or phenylephrine, are rapidly effective but should *not* be used for more than a few days to prevent rebound congestion. Withdrawal of the medication after prolonged use leads to **rhinitis medicamentosa,** an almost addictive need for continuous usage. Treatment of rhinitis medicamentosa requires mandatory cessation of the sprays, and this is often extremely frustrating for patients. Topical intranasal corticosteroids (eg, flunisolide, 2 sprays in each nostril twice daily), intranasal anticholinergic (ipratropium 0.06% nasal spray, 2–3 sprays every 8 hours as needed), or a short tapering course of oral prednisone may help during the withdrawal process.

Complications

Other than mild eustachian tube dysfunction or transient middle ear effusion, complications of viral rhinitis are unusual. Secondary acute bacterial rhinosinusitis is a well-accepted complication of acute viral rhinitis and is suggested by persistence of symptoms beyond 10 days with purulent green or yellow nasal secretions and unilateral facial or dental pain.

Dhama K et al. Coronavirus disease 2019-COVID-19. Clin Microbiol Rev. 2020;33:e00028. [PMID: 32580969]

2. Acute Rhinosinusitis (Rhinosinusitis)

ESSENTIALS OF DIAGNOSIS

- Acute onset of symptoms.
- Purulent yellow-green nasal discharge or expectoration.
- Facial pain or pressure over the affected sinus or sinuses.
- Nasal obstruction.
- Associated cough, malaise, fever, and headache.

General Considerations

Compared with viral rhinitis, acute bacterial rhinosinusitis infections are uncommon, but they still affect nearly 20 million Americans annually and account for over 2 billion dollars in health care expenditures. Acute bacterial rhinosinusitis is believed to be the result of impaired mucociliary clearance, inflammation of the nasal cavity mucosa, and obstruction of the ostiomeatal complex. Edematous mucosa causes obstruction of the complex, resulting in the accumulation of mucus in the sinus cavity that becomes secondarily infected by bacteria. The largest of these ostiomeatal complexes is deep to the middle turbinate in the middle meatus. This complex is actually a confluence of complexes draining the maxillary, ethmoid, and frontal sinuses. The sphenoid drains from a separate complex between the septum and superior turbinate.

The typical pathogens of bacterial rhinosinusitis are *S pneumoniae*, other streptococci, *H influenzae,* and less commonly, *S aureus* and *Moraxella catarrhalis.* Pathogens vary regionally in both prevalence and drug resistance; about 25% of healthy asymptomatic individuals may, if sinus aspirates are cultured, harbor such bacteria as well.

Clinical Findings

A. Symptoms and Signs

There are no agreed-upon criteria for the diagnosis of acute bacterial rhinosinusitis in adults. Major symptoms include purulent nasal drainage, nasal obstruction or congestion, facial pain/pressure, altered smell, cough, and fever. Minor symptoms include headache, otalgia, halitosis, dental pain, and fatigue. Many of the more specific symptoms and signs relate to the affected sinus(es). Bacterial rhinosinusitis can be distinguished from viral rhinitis by persistence of symptoms for more than 10 days after onset or worsening of symptoms within 10 days after initial improvement. Acute rhinosinusitis is defined as lasting less than 4 weeks, and subacute rhinosinusitis, as lasting 4–12 weeks.

Acute maxillary sinusitis is the most common form of acute bacterial rhinosinusitis because the maxillary is the largest sinus with a single drainage pathway that is easily obstructed. Unilateral facial fullness, pressure, and tenderness over the cheek are common symptoms, but may not always be present. Pain may refer to the upper incisor and canine teeth via branches of the trigeminal nerve, which traverse the floor of the sinus. Purulent nasal drainage should be noted with nasal airway obstruction or facial pain (pressure). Maxillary sinusitis may result from dental infection, and teeth that are tender should be carefully examined for signs of abscess. Drainage of the periapical abscess or removal of the diseased tooth typically resolves the sinus infection.

Acute ethmoiditis in adults is often accompanied by maxillary sinusitis, and symptoms are similar to those described above. Localized ethmoid sinusitis may present with pain and pressure over the high lateral wall of the nose between the eyes that may radiate to the orbit.

Sphenoid sinusitis is usually seen in the setting of pansinusitis or infection of all the paranasal sinuses on at least one side. The patient may complain of a headache "in the middle of the head" and often points to the vertex.

Acute frontal sinusitis may cause pain and tenderness of the forehead. This is most easily elicited by palpation of the orbital roof just below the medial end of the eyebrow.

Hospital-associated sinusitis is a form of acute bacterial rhinosinusitis that may present without the usual symptoms. Instead, it may be a cause of fever in critically ill patients. It is often associated with prolonged presence of a nasogastric or, rarely, nasotracheal tube causing nasal mucosal inflammation and ostiomeatal complex obstruction. Pansinusitis on the side of the tube is common on imaging studies.

B. Imaging

The diagnosis of acute bacterial rhinosinusitis can usually be made on clinical grounds alone. Although more sensitive than clinical examination, routine radiographs are not cost-effective and are *not* recommended by the Agency for Health Care Policy and Research or American Association of Otolaryngology Guidelines. Consensus guidelines recommend imaging when clinical criteria are difficult to evaluate, when the patient does not respond to appropriate therapy or has been treated repeatedly with antibiotics, when intracranial involvement or cerebrospinal fluid rhinorrhea is suspected, when complicated dental infection is suspected, or when symptoms of more serious infection are noted.

When necessary, noncontrast screening coronal CT scans are more cost-effective and provide more information than conventional sinus films. CT provides a rapid and effective means to assess all of the paranasal sinuses, identify areas of greater concern (such as bony dehiscence, periosteal elevation, or maxillary tooth root exposure within the sinus), and speed appropriate therapy.

CT scans are reasonably sensitive but are not specific. Swollen soft tissue and fluid may be difficult to distinguish when opacification of the sinus is due to other conditions, such as chronic rhinosinusitis, nasal polyposis, or mucus retention cysts. Sinus abnormalities can be seen in most patients with an upper respiratory infection, while bacterial rhinosinusitis develops in only 2%.

If malignancy, intracranial extension, or opportunistic infection is suspected, MRI with gadolinium should be ordered instead of, or in addition to, CT. MRI will distinguish tumor from fluid, inflammation, and inspissated mucus far better than CT, and will better delineate tumor extent (eg, involvement of adjacent structures, such as the orbit, skull base, and palate). Bone destruction can be demonstrated as well by MRI as by CT.

Treatment

All patients with acute bacterial rhinosinusitis should have careful evaluation of pain. For symptom reduction in viral rhinitis and bacterial rhinosinusitis without complication, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012 recommends NSAIDs, saline nasal sprays, and nasal decongestants (pseudoephedrine, 30–60 mg every 6 hours, up to 240 mg/day; nasal oxymetazoline, 0.05% or oxymetazoline, 0.05–0.1%, one or two sprays in each nostril every 6–8 hours for up to 3 days). In cases of suspected bacterial rhinosinusitis, intranasal corticosteroids (eg, high-dose mometasone furoate 200 mcg each nostril twice daily for 21 days) have demonstrated efficacy in reducing nasal symptoms and are recommended. Other medications, such as mucolytics, vitamin C, probiotics, and antihistamines, have not demonstrated efficacy in the management of acute rhinosinusitis.

Antibiotic therapy should be reserved for complicated or protracted acute bacterial rhinosinusitis. Between 40% and 69% of patients with acute bacterial rhinosinusitis improve symptomatically within 2 weeks without antibiotic therapy. Antibiotic treatment is controversial in uncomplicated cases of clinically diagnosed acute bacterial rhinosinusitis because only 5% of patients will note a shorter duration of illness with treatment, and antibiotic treatment is associated with nearly twice the number of adverse events compared with placebo. Antibiotics may be considered when symptoms last more than 10 days or when symptoms (including fever, facial pain, and swelling of the face) are severe or when cases are complicated (such as immunodeficiency). In these patients, administration of antibiotics does reduce the incidence of clinical failure by 50% and represents the most cost-effective treatment strategy.

Selection of antibiotics is usually empiric and based on a number of factors, including regional patterns of antibiotic resistance, antibiotic allergy, cost, and patient tolerance. For adults younger than 65 years with mild to moderate acute bacterial rhinosinusitis, the recommended first-line therapy is amoxicillin-clavulanate (500 mg/125 mg orally three times daily or 875 mg/125 mg orally twice daily for 5–7 days), or in those with severe sinusitis, high-dose amoxicillin-clavulanate (2000 mg/125 mg extended-release orally twice daily for 7–10 days). In patients with a high risk for penicillin-resistant *S pneumoniae* (age over 65 years, hospitalization in the prior 5 days, antibiotic use in the prior month, immunocompromised status, multiple comorbidities, or severe sinus infection), the recommended first-line therapy is the high-dose amoxicillin-clavulanate option (2000 mg/125 mg extended-release orally twice daily for 7–10 days). For those with penicillin allergy or hepatic impairment, doxycycline (100 mg orally twice daily or 200 mg orally once daily for 5–7 days) or clindamycin (150–300 mg every 6 hours) plus a cephalosporin (cefixime 400 mg orally once daily or cefpodoxime proxetil 200 mg orally twice daily) for 10 days are options. Macrolides, trimethoprim-sulfamethoxazole, and second- or third-generation cephalosporins are not recommended for empiric therapy. Dupilumab, a monoclonal antibody with inhibition of IL-4 and IL-13, is approved for patients with chronic sinusitis with nasal polyposis.

Hospital-associated infections in critically ill patients are treated differently from community-acquired infections. Removal of a nasogastric tube and improved nasal hygiene (nasal saline sprays, humidification of supplemental nasal oxygen, and nasal decongestants) are critical interventions and often curative in mild cases without aggressive antibiotic use. Endoscopic or transantral cultures may help direct medical therapy in complicated cases. In addition, broad-spectrum antibiotic coverage directed at *P aeruginosa, S aureus* (including methicillin-resistant strains), and anaerobes may be required.

Complications

Local complications of acute bacterial rhinosinusitis include orbital cellulitis and abscess, osteomyelitis, cavernous sinus thrombosis, and intracranial extension.

Orbital complications typically occur by extension of ethmoid sinusitis through the lamina papyracea, a thin layer of bone that comprises the medial orbital wall. Any change in the ocular examination necessitates immediate CT imaging. Extension in this area may cause orbital cellulitis leading to proptosis, gaze restriction, and orbital pain. Select cases are responsive to intravenous antibiotics, with or without corticosteroids, and should be managed in close conjunction with an ophthalmologist or otolaryngologist, or both. Extension through the lamina papyracea can also lead to subperiosteal abscess formation (orbital abscess). Such abscesses cause marked proptosis, ophthalmoplegia, and pain with medial gaze. While some cases respond to antibiotics, such findings should prompt an immediate referral to a specialist for consideration of decompression and evacuation. Failure to intervene quickly may lead to permanent visual impairment and a "frozen globe."

Osteomyelitis requires prolonged antibiotics as well as removal of necrotic bone. The frontal sinus is most commonly affected, with bone involvement suggested by a tender swelling of the forehead (**Pott puffy tumor**). Following treatment, secondary cosmetic reconstructive procedures may be necessary.

Intracranial complications of sinusitis can occur either through hematogenous spread, as in cavernous sinus thrombosis and meningitis, or by direct extension, as in epidural and intraparenchymal brain abscesses. Fortunately, they are rare today. Cavernous sinus thrombosis is heralded by ophthalmoplegia, chemosis, and visual loss; the diagnosis is most commonly confirmed by MRI. When identified early, cavernous sinus thrombosis typically responds to intravenous antibiotics. Frontal epidural and intracranial abscesses are often clinically silent, but may present with altered mental status, persistent fever, or severe headache.

When to Refer

Failure of acute bacterial rhinosinusitis to resolve after an adequate course of oral antibiotics necessitates referral to an otolaryngologist for evaluation. Endoscopic cultures may direct further treatment choices. Nasal endoscopy and CT scan are indicated when symptoms persist longer than 4–12 weeks. Any patients with suspected extension of disease outside the sinuses should be evaluated urgently by an otolaryngologist and imaging should be obtained.

When to Admit

- Facial swelling and erythema indicative of facial cellulitis.
- Proptosis.
- Vision change or gaze abnormality indicative of orbital cellulitis.
- Abscess or cavernous sinus involvement.
- Mental status changes suggestive of intracranial extension.
- Failure to respond to appropriate first-line treatment or symptoms persisting longer than 4 weeks.

Hoy SM. Dupilumab: a review in chronic rhinosinusitis with nasal polyps. Drugs. 2020;80:711. [PMID: 32240527]

3. Nasal Vestibulitis & *S aureus* Nasal Colonization

Inflammation of the nasal vestibule may result from folliculitis of the hairs that line this orifice and is usually the result of nasal manipulation or hair trimming. Systemic antibiotics effective against *S aureus* (such as dicloxacillin, 250 mg orally four times daily for 7–10 days) are indicated. Topical mupirocin 2% nasal ointment (applied two or three times daily) also may be a helpful addition and may prevent future occurrences. If recurrent, the addition of rifampin (10 mg/kg orally twice daily for the last 4 days of dicloxacillin treatment) may eliminate the *S aureus* carrier state. If a furuncle exists, it should be incised and drained, preferably intranasally. Adequate treatment of these infections is important to prevent retrograde spread of infection through valveless veins into the cavernous sinus and intracranial structures.

S aureus is the leading nosocomial pathogen, and nasal carriage is a well-defined risk factor in the development and spread of nosocomial infections. Nasal and extranasal methicillin-resistant *S aureus* (MRSA) colonizations are associated with a 30% risk of developing an invasive MRSA infection during hospital stays. While the vast majority have no vestibulitis symptoms, screening by nasal swabs and PCR-based assays has demonstrated a 30% rate of *S aureus* colonization in hospital patients and an 11% rate of MRSA colonization in ICU patients. Elimination of the carrier state is challenging, but studies of mupirocin 2% nasal ointment application with chlorhexidine facial washing (40 mg/mL) twice daily for 5 days have demonstrated decolonization in 39% of patients.

Septimus EJ. Nasal decolonization: what antimicrobials are most effective prior to surgery? Am J Infect Control. 2019;47S:A53. [PMID: 31146851]

4. Invasive Fungal Sinusitis

Invasive fungal sinusitis is rare and includes both rhinocerebral mucormycosis (*Mucor, Absidia,* and *Rhizopus* spp.) and other invasive fungal infections, such as *Aspergillus*. The fungus spreads rapidly through vascular channels and may be lethal if not detected early. Patients with mucormycosis almost invariably have some degree of immunocompromise, such as diabetes mellitus, long-term corticosteroid therapy, neutropenia associated with chemotherapy for hematologic malignancy, or end-stage renal disease. Occasional cases of sinonasal infection with *Aspergillus* spp. have been reported in patients with untreated HIV/AIDS. The initial symptoms may be similar to those of acute bacterial rhinosinusitis, although facial pain is often more severe.

Nasal drainage is typically clear or straw-colored, rather than purulent, and visual symptoms may be noted at presentation in the absence of significant nasal findings. On examination, the classic finding of mucormycosis is a black eschar on the middle turbinate, but this finding is not universal and may not be apparent if the infection is deep or high within the nasal bones. Often the mucosa appears normal or simply pale and dry. This may be noted on the hard palate as well. Early diagnosis requires suspicion of the disease and nasal biopsy with silver stains, revealing broad nonseptate hyphae within tissues and necrosis with vascular occlusion. Imaging, such as CT or MRI, may initially show only soft tissue changes. Consequently, biopsy and ultimate debridement should be based on the clinical setting rather than radiographic demonstration of bony destruction or intracranial changes.

Invasive fungal sinusitis represents a medical and surgical emergency. Once recognized, voriconazole may be started by intravenous infusion, and prompt wide surgical debridement is indicated for patients with reversible immune deficiency (eg, poorly controlled hyperglycemia in diabetes). Other antifungals, including amphotericin or the less nephrotoxic lipid-based amphotericin B (Ambisome) and caspofungin, are alternatives to voriconazole and may be added to voriconazole depending on the fungus. Surgical management, while necessary for any possibility of cure, often results in tremendous disfigurement and functional deficits (eg, often resulting in the loss of at least one eye). Even with early diagnosis and immediate appropriate intervention, the prognosis is guarded. In persons with diabetes, the mortality rate is about 20%. If kidney disease is present or develops, mortality is over 50%; in the setting of AIDS or hematologic malignancy with neutropenia, mortality approaches 100%. Whether to undertake aggressive surgical management should be considered carefully because many patients are gravely ill at the time of diagnosis, and overall disease-specific survival is only about 57%.

Craig JR. Updates in management of acute invasive fungal rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2019;27:29. [PMID: 30585877]

Kashkouli MB et al. Outcomes and factors affecting them in patients with rhino-orbito-cerebral mucormycosis. Br J Ophthalmol. 2019;103:1460. [PMID: 30514712]

ALLERGIC RHINITIS

ESSENTIALS OF DIAGNOSIS

- Clear rhinorrhea, sneezing, tearing, eye irritation, and pruritus.
- Associated symptoms include cough, bronchospasm, and eczematous dermatitis.
- Environmental allergen exposure in the presence of allergen-specific IgE.

General Considerations

Allergic rhinitis is very common in the United States with population studies reporting a prevalence of 20–30% of adults and up to 40% of children. Allergic rhinitis adversely affects school and work performance, costing about $6 billion annually in the United States through direct costs of therapy as well as the indirect costs of sleep deprivation, fatigue and reduced productivity, or absenteeism. Seasonal allergic rhinitis is most commonly caused by pollens and spores. Flowering shrub and tree pollens are most common in the spring, flowering plants and grasses in the summer, and ragweed and molds in the fall. Interestingly, climate change may have an impact on the occurrence of allergic rhinitis since increased temperature and carbon dioxide exposure cause increased pollen production in ragweed plants and since the extended duration of summer correlates with longer periods of pollen production in these and other flowering weeds. Dust, household mites, air pollution, and pet dander may produce year-round symptoms, termed "perennial rhinitis."

Clinical Findings

The symptoms of "hay fever" are similar to those of viral rhinitis but are usually persistent and may show seasonal variation. Nasal symptoms are often accompanied by eye irritation, pruritus, conjunctival erythema, and excessive tearing. Many patients have a strong family history of atopy or allergy.

The clinician should be careful to distinguish allergic rhinitis from other types of nonallergic rhinitis. **Vasomotor rhinitis** (sometimes called **senile rhinitis**) is caused by increased sensitivity of the vidian nerve and is a common cause of clear rhinorrhea in elderly persons. Often patients will report that they have troubling rhinorrhea in response to numerous nasal stimuli, including warm or cold air, odors or scents, light, or particulate matter. Other types of rhinitis, including gustatory, atrophic, and drug-induced rhinorrhea, have also been described.

On physical examination, the mucosa of the turbinates is usually pale or violaceous because of venous engorgement. This is in contrast to the erythema of viral rhinitis. Nasal polyps, which are yellowish boggy masses of hypertrophic mucosa, are associated with long-standing allergic rhinitis.

Treatment

A. Intranasal Corticosteroids

Intranasal corticosteroid sprays remain the mainstay of treatment of allergic rhinitis. They are more effective—and frequently less expensive—than nonsedating antihistamines, though patients should be reminded that there may be a delay in onset of relief of 2 or more weeks. Corticosteroid sprays may also shrink hypertrophic nasal mucosa and nasal polyps, thereby providing an improved nasal airway and ostiomeatal complex drainage. Because of this effect, intranasal corticosteroids are critical in treating allergy in patients prone to recurrent acute bacterial rhinosinusitis or chronic rhinosinusitis. Available preparations include

beclomethasone (42 mcg/spray twice daily per nostril), flunisolide (25 mcg/spray twice daily per nostril), mometasone furoate (200 mcg once daily per nostril), budesonide (100 mcg twice daily per nostril), and fluticasone propionate (200 mcg once daily per nostril). All are considered equally effective. Probably the most critical factors are compliance with regular use and proper introduction into the nasal cavity. In order to deliver medication to the region of the middle meatus, proper application involves holding the bottle straight up with the head tilted forward and pointing the bottle toward the ipsilateral ear when spraying. Side effects are limited, the most annoying being epistaxis (perhaps related to incorrect delivery of the drug toward the nasal septum).

B. Antihistamines

Antihistamines offer temporary, but immediate, control of many of the most troubling symptoms of allergic rhinitis. Effective oral antihistamines include nonsedating loratadine (10 mg once daily), desloratadine (5 mg once daily), and fexofenadine (60 mg twice daily or 120 mg once daily), and minimally sedating cetirizine (10 mg once daily). Brompheniramine or chlorpheniramine (4 mg orally every 6–8 hours, or 8–12 mg orally every 8–12 hours as a sustained-release tablet) and clemastine (1.34–2.68 mg orally twice daily) may be less expensive but are usually associated with some drowsiness. The safety and efficacy of the newer, less-sedating antihistamines is so compelling that one of them, the H_1-receptor antagonist nasal spray azelastine (1–2 sprays per nostril daily), is now included in the treatment guidelines of many consensus statements; however, some patients object to its bitter taste. Other side effects of oral antihistamines besides sedation include xerostomia and antihistamine tolerance (with eventual return of allergy symptoms despite initial benefit after several months of use). In such patients, typically those with perennial allergy, alternating effective antihistamines periodically can control symptoms over the long term. The FDA has approved a nasal spray containing the corticosteroid mometasone (25 mcg) and the H_1-inhibitor olopatidine hydrochloride (665 mcg) (Ryaltris) for seasonal allergic rhinitis. The dosage is 2 sprays in each nostril daily. The long-term efficacy of this medication is not yet known.

C. Adjunctive Treatment Measures

Antileukotriene medications, such as montelukast (10 mg/day orally), alone or with cetirizine (10 mg/day orally) or loratadine (10 mg/day orally), may improve nasal rhinorrhea, sneezing, and congestion. Cromolyn sodium and sodium nedocromil may be useful adjunct agents for allergic rhinitis. They work by stabilizing mast cells and preventing proinflammatory mediator release. As topical agents, they have very few side effects, but they must be initiated *well before* allergen exposure (up to 4 weeks before). The most useful form of cromolyn is probably the ophthalmologic preparation placed dropwise into the nasal cavity. Intranasal cromolyn is cleared rapidly and must be administered four times daily for continued symptom relief. In practice, it is not nearly as effective as inhaled corticosteroid.

Intranasal anticholinergic agents, such as ipratropium bromide 0.03% or 0.06% sprays (42–84 mcg per nostril three times daily), may be helpful adjuncts when rhinorrhea is a major symptom. They are not as effective for treating allergic rhinitis but are more useful for treating vasomotor rhinitis.

Avoiding or reducing exposure to airborne allergens is the most effective means of alleviating symptoms of allergic rhinitis. Depending on the allergen, this can be extremely difficult. Maintaining an allergen-free environment by covering pillows and mattresses with plastic covers, substituting synthetic materials (foam mattress, acrylics) for animal products (wool, horsehair), and removing dust-collecting household fixtures (carpets, drapes, bedspreads, wicker) is worth the attempt to help more troubled patients. Air purifiers and dust filters may also aid in maintaining an allergen-free environment. Nasal saline irrigations are a useful adjunct in the treatment of allergic rhinitis to mechanically flush the allergens from the nasal cavity. When symptoms are extremely bothersome, a search for offending allergens may prove helpful. This can either be done by serum radioallergosorbent test (RAST) testing or skin testing by an allergist.

In some cases, allergic rhinitis symptoms are inadequately relieved by medication and avoidance measures. Often, such patients have a strong family history of atopy and may also have lower respiratory manifestations, such as allergic asthma. Referral to an otolaryngologist or allergist for immunotherapy may be appropriate. Such treatment involves proper identification of offending allergens, progressively increasing doses of allergen(s), and eventual maintenance dose administration over a period of 3–5 years. Immunotherapy has been proven to reduce circulating IgE levels in patients with allergic rhinitis and reduce the need for allergy medications. Both subcutaneous and topical immunotherapy have been shown to be effective in the long-term treatment of refractory allergic rhinitis.

Fein MN et al. CSACI position statement: newer generation H_1-antihistamines are safer than first-generation H_1-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria. Allergy Asthma Clin Immunol. 2019;15:61. [PMID: 3158299]

Meltzer EO et al. Meta-analyses of the efficacy of pharmacotherapies and sublingual allergy immunotherapy tablets for allergic rhinitis in adults and children. Rhinology. 2021;59:422. [PMID: 34463311]

OLFACTORY DYSFUNCTION

ESSENTIALS OF DIAGNOSIS

- Subjective diminished smell or taste sensation.
- Lack of objective nasal obstruction.
- Objective decrease in olfaction demonstrated by testing.

General Considerations

Anatomic blockage of the nasal cavity with subsequent airflow disruption is the most common cause of olfactory dysfunction (hyposmia or anosmia). Polyps, septal deformities, and nasal tumors may be the cause. Due to localized inflammation, transient olfactory dysfunction often accompanies the common cold, nasal allergies, and perennial rhinitis through changes in the nasal and olfactory epithelium. About 20% of olfactory dysfunction is idiopathic, although it often follows a viral illness.

CNS neoplasms, especially those that involve the olfactory groove or temporal lobe, also may affect olfaction and should be considered in patients with no other explanation for their hyposmia. Head trauma is also a rare but severe cause of olfactory dysfunction due to shearing of the olfactory sensory cells. Head trauma accounts for less than 5% of cases of hyposmia but is more commonly associated with anosmia than with hyposmia. Absent, diminished, or distorted smell has been reported in a wide variety of endocrine, nutritional, and nervous disorders.

Clinical Findings

Evaluation of olfactory dysfunction should include a thorough history of systemic illnesses and medication use as well as a physical examination focusing on the nose and nervous system. Nasal obstruction (from polyps, trauma, foreign bodies, or nasal masses) can cause functional hyposmia. Most clinical offices are not set up to test olfaction, but such tests may at times be worthwhile if only to assess whether a patient possesses any sense of smell at all. The University of Pennsylvania Smell Identification Test (UPSIT) is available commercially and is a simple, self-administered "scratch-and-sniff" test that is useful in differentiating hyposmia, anosmia, and malingering.

Treatment

Olfactory dysfunction secondary to nasal polyposis, obstruction, and chronic rhinosinusitis may respond to surgically removing the anatomic blockage, as with endoscopic sinus surgery. Unfortunately, there is no specific treatment for primary disruption of olfaction; some disturbances spontaneously resolve. The degree of olfactory dysfunction is the greatest predictor of recovery, with less severe olfactory dysfunction recovering at a much higher rate. In permanent olfactory dysfunction, counseling should be offered about seasoning foods (such as using pepper that stimulates the trigeminal as well as olfactory chemoreceptors, rather than table salt) and safety issues (such as installing home smoke alarms and using electric rather than gas appliances).

Kasiri H et al. Mometasone furoate nasal spray in the treatment of patients with COVID-19 olfactory dysfunction: a randomized, double blind clinical trial. Int Immunopharmacol. 2021;98:107871. [PMID: 34147912]

Roh D et al. The association between olfactory dysfunction and cardiovascular disease and its risk factors in middle-aged and older adults. Sci Rep. 2021;11:1248. [PMID: 33441955]

EPISTAXIS

ESSENTIALS OF DIAGNOSIS

- Bleeding from a unilateral anterior nasal cavity along the septum is most common.
- Most cases may be successfully treated by direct pressure on the bleeding site for 15 minutes. When this is inadequate, topical sympathomimetics and various nasal tamponade methods are usually effective.
- Posterior, bilateral, or large-volume epistaxis should be triaged immediately to a specialist in a critical care setting.

General Considerations

Epistaxis is an extremely common problem in the primary care setting. Bleeding is most common in the anterior septum where a confluence of veins creates a superficial venous plexus (Kiesselbach plexus). Predisposing factors include nasal trauma (nose picking, foreign bodies, forceful nose blowing), rhinitis, nasal mucosal drying from low humidity or supplemental nasal oxygen, deviation of the nasal septum, atherosclerotic disease, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), inhaled nasal cocaine (or other drugs), and alcohol abuse. Poorly controlled hypertension is associated with epistaxis. Anticoagulation or antiplatelet medications may be associated with a higher incidence, more frequent recurrence, and greater difficulty in control of epistaxis, but they do not cause it.

Clinical Findings

Laboratory assessment of bleeding parameters may be indicated, especially in recurrent epistaxis. Once the acute episode has passed, careful examination of the nose and paranasal sinuses is indicated to rule out neoplasia and hereditary hemorrhagic telangiectasia. Repeated evaluation for diagnosis and treatment of clinically significant hypertension should be performed following control of epistaxis and removal of any packing.

Treatment

Most cases of anterior epistaxis may be successfully treated by direct pressure on the site by compression of the nares continuously for 15 minutes. Venous pressure is reduced in the sitting position, and slight leaning forward. Positioning the head backwards is not recommended because this may result in blood going toward the airway, resulting in possible aspiration. Similarly, pinching the bridge of the nose is generally ineffective as the origin of bleeding typically occurs at the tip. Short-acting topical nasal decongestants (eg, phenylephrine, 0.125–1% solution, one or two sprays or oxymetazoline), which act as vasoconstrictors, may also help. When the bleeding does not readily subside, the nose

should be examined, using good illumination and suction, in an attempt to locate the bleeding site. When directly visible, the bleeding site may be cauterized with silver nitrate, diathermy, or electrocautery. A supplemental patch of Surgicel or Gelfoam may be helpful with a moisture barrier, such as petroleum-based ointment, to prevent drying and crusting.

Occasionally, a site of bleeding may be inaccessible to direct control, or attempts at direct control may be unsuccessful. In such cases, there are a number of alternatives. When the site of bleeding is anterior, a hemostatic sealant, pneumatic or other nasal tamponade, or anterior packing may suffice as the latter may be accomplished with several feet of lubricated iodoform packing systematically placed in the floor of the nose and then the vault of the nose.

About 5% of nasal bleeding originates in the posterior nasal cavity, commonly associated with atherosclerotic disease and hypertension. In such cases, it may be necessary to consult an otolaryngologist for a pack to occlude the choana before placing a pack anteriorly. In emergency settings, double balloon packs (Epistat) may facilitate rapid control of bleeding with little or no mucosal trauma. Because such packing is uncomfortable, bleeding may persist, and vasovagal syncope is possible, hospitalization for monitoring and stabilization is indicated. Posterior nasal packing is quite uncomfortable and may require an opioid analgesic for pain control.

Surgical management of epistaxis, through ligation of the nasal arterial supply (internal maxillary artery and ethmoid arteries) is indicated when direct pressure and nasal packing fail. The most common approach to surgical treatment is endoscopic sphenopalatine artery ligation. This method has a reported efficacy of 73–100% in studies; however, it may miss bleeds caused by the ethmoid arterial supply. Alternatively, endovascular epistaxis control is highly effective (75–92%) and can address all sources of intranasal bleeding except those from the anterior ethmoid artery. Its use may be reserved for when a surgical approach fails because it is associated with a 1.1–1.5% risk of stroke.

After control of epistaxis, the patient is advised to avoid straining and vigorous exercise for several days. Nasal saline should be applied to the packing frequently to keep the packing moist. Avoidance of hot or spicy foods and tobacco is also advisable, since these may cause nasal vasodilation. Avoiding nasal trauma, including nose picking, is an obvious necessity. Lubrication with petroleum jelly or bacitracin ointment and increased home humidity may also be useful ancillary measures. Finally, antistaphylococcal antibiotics (eg, cephalexin, 500 mg orally four times daily, or clindamycin, 150 mg orally four times daily) generally are indicated to reduce the risk of toxic shock syndrome developing while the packing remains in place (at least 5 days).

When to Refer

- Patients with recurrent epistaxis, large-volume epistaxis, and episodic epistaxis with associated nasal obstruction should be referred to an otolaryngologist for endoscopic evaluation and possible imaging.
- Those with ongoing bleeding beyond 15 minutes should be taken to a local emergency department if the clinician is not prepared to manage acute epistaxis.

D'Aguanno V et al. Clinical recommendations for epistaxis management during the COVID-19 pandemic. Otolaryngol Head Neck Surg. 2020;163:75. [PMID: 32366173]

Tran QK et al. Prophylactic antibiotics for anterior nasal packing in emergency department: a systematic review and meta-analysis of clinically-significant infections. Am J Emerg Med. 2020;38:983. [PMID: 31839514]

Tunkel DE et al. Clinical practice guideline: nosebleed (epistaxis) executive summary. Otolaryngol Head Neck Surg. 2020;162:8. [PMID: 31910122]

NASAL TRAUMA

The nasal pyramid is the most frequently fractured bone in the body. Fracture is suggested by crepitance or palpably mobile bony segments. Epistaxis and pain are common, as are soft-tissue hematomas ("black eye"). It is important to make certain that there is no palpable step-off of the infraorbital rim, which would indicate the presence of a zygomatic complex fracture. Radiologic confirmation may at times be helpful but is not necessary in uncomplicated nasal fractures. It is also important to assess for possible concomitant additional facial, spine, pulmonary, or intracranial injuries when the circumstances of injury are suggestive, as in the case of automobile and motorcycle accidents.

Treatment is aimed at maintaining long-term nasal airway patency and cosmesis. Closed reduction can be performed under local or general anesthesia; closed reduction under general anesthesia appears to afford better patient satisfaction and decreased need for subsequent revision septoplasty or rhinoplasty.

Intranasal examination should be performed in all cases to rule out septal hematoma, which appears as a widening of the anterior septum, visible just posterior to the columella. The septal cartilage receives its only nutrition from its closely adherent mucoperichondrium. An untreated subperichondrial hematoma will result in loss of the nasal cartilage with resultant saddle nose deformity, septal perforation, or both. Septal hematomas may become infected, with *S aureus* most commonly, and should be drained with an incision in the inferior mucoperichondrium on both sides. The drained fluid should be sent for culture.

Packing for 2–5 days is often helpful to help prevent reformation of the hematoma. Antibiotics with antistaphylococcal efficacy (eg, cephalexin, 500 mg four times daily, or clindamycin, 150 mg four times daily) should be given for 3–5 days or the duration of the packing to reduce the risk of toxic shock syndrome.

TUMORS & GRANULOMATOUS DISEASE

1. Benign Nasal Tumors

A. Nasal Polyps

Nasal polyps are pale, edematous, mucosally covered masses commonly seen in patients with allergic rhinitis. They may result in chronic nasal obstruction and a

diminished sense of smell. In patients with nasal polyps and a history of asthma, aspirin should be avoided because it may precipitate a severe episode of bronchospasm, known as **triad asthma** (Samter triad). Such patients may have an immunologic salicylate sensitivity.

Use of topical intranasal corticosteroids improves the quality of life in patients with nasal polyposis and chronic rhinosinusitis. Initial treatment with topical nasal corticosteroids (see Allergic Rhinitis section for specific medications) for 1–3 months is usually successful for small polyps and may reduce the need for operation. A short course of oral corticosteroids (eg, prednisone, 6-day course using 21 [5-mg] tablets: 6 tablets [30 mg] on day 1 and tapering by 1 tablet [5 mg] each day) may also be of benefit, but when polyps are massive or medical management is unsuccessful obstructing polyps may be removed surgically. Polyps may readily be removed using endoscopic sinus surgery techniques. It may be necessary to remove polyps from the ethmoid, sphenoid, and maxillary sinuses to provide longer-lasting relief and open the affected sinuses. Intranasal corticosteroids should be continued following polyp removal to prevent recurrence, and the clinician should consider allergen testing to determine the offending allergen and avoidance measures.

Brescia G. Role of blood inflammatory cells in chronic rhinosinusitis with nasal polyps. Acta Otolaryngol. 2019;139:48. [PMID: 30686139]

Song WJ et al. Chronic rhinosinusitis with nasal polyps in older adults: clinical presentation, pathophysiology, and comorbidity. Curr Allergy Asthma Rep. 2019;19:46. [PMID: 31486905]

B. Inverted Papillomas

Inverted papillomas are benign tumors caused by HPV that usually arise on the lateral nasal wall. They present with unilateral nasal obstruction and occasionally hemorrhage. They are often easily seen on anterior rhinoscopy as cauliflower-like growths in or around the middle meatus. Because squamous cell carcinoma is seen in about 10% of inverted or schneiderian papillomas, complete excision is strongly recommended. This usually requires an endoscopic medial maxillectomy. While rare, very extensive disease may require an open inferior or total maxillectomy for complete removal. Because recurrence rates for inverted papillomas are reported to be as high as 20%, subsequent clinical and radiologic follow-up is imperative. All excised tissue (not just a portion) should be carefully reviewed by the pathologist to be sure no carcinoma is present.

Peng R et al. Outcomes of sinonasal inverted papilloma resection by surgical approach: an updated systematic review and meta-analysis. Int Forum Allergy Rhinol. 2019;9:573. [PMID: 30748098]

2. Malignant Nasopharyngeal & Paranasal Sinus Tumors

Though rare, malignant tumors of the nose, nasopharynx, and paranasal sinuses are quite problematic because they tend to remain asymptomatic until late in their course. Squamous cell carcinoma is the most common cancer found in the sinuses and nasopharynx. It is especially common in the nasopharynx, where it obstructs the eustachian tube and results in serous otitis media. Nasopharyngeal carcinoma (nonkeratinizing squamous cell carcinoma or lymphoepithelioma) is usually associated with elevated IgA antibody to the viral capsid antigen of the Epstein-Barr virus (EBV). It is particularly common in patients of southern Chinese descent and has a weaker association with tobacco exposure than other head and neck squamous cell carcinomas. Adenocarcinomas, mucosal melanomas, sarcomas, and non-Hodgkin lymphomas are less commonly encountered neoplasms of this area.

Early symptoms are nonspecific, mimicking those of rhinitis or sinusitis. Unilateral nasal obstruction, otitis media, and discharge are common, with pain and recurrent hemorrhage often clues to the diagnosis of cancer. **All adults with persistent unilateral nasal symptoms or new otitis media should be thoroughly evaluated with nasal endoscopy and nasopharyngoscopy.** A high index of suspicion remains a key to early diagnosis of these tumors. Patients often present with advanced symptoms, such as proptosis, expansion of a cheek, or ill-fitting maxillary dentures. Malar hypesthesia, due to involvement of the infraorbital nerve, is common in maxillary sinus tumors. Biopsy is necessary for definitive diagnosis, and MRI is the best imaging study to delineate the extent of disease and plan appropriate surgery and radiation.

Treatment depends on the tumor type and the extent of disease. Early stage disease may be treated with radiation therapy alone, but advanced nasopharyngeal carcinoma is best treated with concurrent radiation and chemotherapy. Chemoradiation therapy significantly decreases local, nodal, and distant failures and increases progression-free and overall survival in advanced disease. Locally recurrent nasopharyngeal carcinoma in selected cases may be treated with repeat irradiation protocols or surgery with moderate success and a high degree of concern about local wound healing. Other squamous cell carcinomas are best treated—when resectable—with a combination of surgery and irradiation. Cranial base surgery, which can be done endoscopically using image navigation, appears to be an effective modality in improving the overall prognosis in paranasal sinus malignancies eroding the ethmoid roof. Although the prognosis is poor for advanced tumors, the results of treating resectable tumors of paranasal sinus origin have improved with the wider use of skull base resections and intensity-modulated radiation therapy. Cure rates are often 45–60%.

Masarwy R et al. Neoadjuvant PD-1/PD-L1 inhibitors for resectable head and neck cancer: a systematic review and meta-analysis. JAMA Otolaryngol Head Neck Surg. 2021;147:871. [PMID: 34473219]

3. Sinonasal Inflammatory Disease (Granulomatosis with Polyangiitis & Sarcoidosis)

The nose and paranasal sinuses are involved in over 90% of cases of **granulomatosis with polyangiitis**. It is often not realized that involvement at these sites is more common than involvement of lungs or kidneys. Examination shows

bloodstained crusts and friable mucosa. Biopsy, when positive, shows necrotizing granulomas and vasculitis. Other recognized sites of granulomatosis with polyangiitis in the head and neck include the subglottis and the middle ear. For treatment of granulomatosis with polyangiitis, see Chapter 20.

Sarcoidosis commonly involves the paranasal sinuses and is clinically similar to other chronic sinonasal inflammatory processes. Sinonasal symptoms, including rhinorrhea, nasal obstruction, and hyposmia or anosmia, may precede diagnosis of sarcoidosis in other organ systems. Clinically, the turbinates appear engorged with small white granulomas. Biopsy shows classic noncaseating granulomas. Notably, patients with sinonasal involvement generally have more trouble managing sarcoidosis in other organ systems.

Polymorphic reticulosis (midline malignant reticulosis, idiopathic midline destructive disease, lethal midline granuloma)—as the multitude of apt descriptive terms suggests—is not well understood but appears to be a nasal T-cell or NK-cell lymphoma. In contrast to granulomatosis with polyangiitis, involvement is limited to the mid-face, and there may be extensive bone destruction. Many destructive lesions of the mucosa and nasal structures labeled as polymorphic reticulosis are in fact non-Hodgkin lymphoma of either NK-cell or T-cell origin. Immunophenotyping, especially for CD56 expression, is essential in the histologic evaluation. Even when apparently localized, these lymphomas have a poor prognosis, with progression and death within a year the rule.

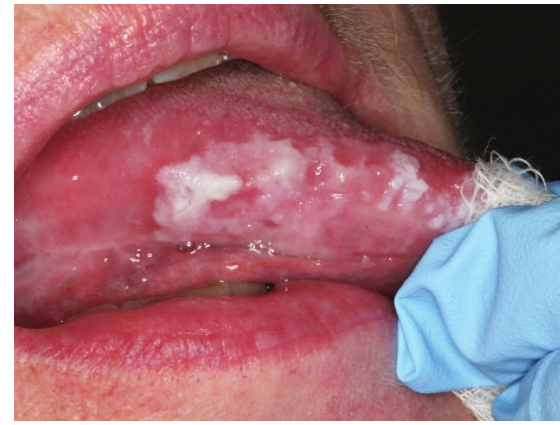
Guzman-Soto MI et al. From head to toe: granulomatosis with polyangiitis. Radiographics. 2021;41:1973. [PMID: 34652975]

DISEASES OF THE ORAL CAVITY & PHARYNX

LEUKOPLAKIA, ERYTHROPLAKIA, LICHEN PLANUS, & AND OROPHARYNGEAL CANCER

ESSENTIALS OF DIAGNOSIS

- **Leukoplakia:** A white lesion that cannot be removed by rubbing the mucosal surface.
- **Erythroplakia:** Similar to leukoplakia except that it has a definite erythematous component.
- **Oral Lichen Planus:** Most commonly presents as lacy leukoplakia but may be erosive; definitive diagnosis requires biopsy.
- **Oral Cancer:** Early lesions appear as leukoplakia or erythroplakia; more advanced lesions will be larger, with invasion into the tongue such that a mass lesion is palpable. Ulceration may be present.
- **Oropharyngeal Cancer:** Unilateral throat masses, such as emanating from the tonsils or base of tongue, typically presenting with painful swallowing and weight loss.



▲ **Figure 8–5.** Leukoplakia with moderate dysplasia on the lateral border of the tongue. (Used, with permission, from Ellen Eisenberg, DMD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Leukoplakic regions range from small to several centimeters in diameter (Figure 8–5). Histologically, they are often hyperkeratoses occurring in response to chronic irritation (eg, from dentures, tobacco, lichen planus); about 2–6%, however, represent either dysplasia or early invasive squamous cell carcinoma. Distinguishing between **leukoplakia** and **erythroplakia** is important because about 90% of cases of erythroplakia are either dysplasia or carcinoma. **Squamous cell carcinoma** accounts for 90% of oral cancer. Alcohol and tobacco use are the major epidemiologic risk factors.

The differential diagnosis may include oral candidiasis, necrotizing sialometaplasia, pseudoepitheliomatous hyperplasia, median rhomboid glossitis, and vesiculoerosive inflammatory disease, such as erosive lichen planus. This should not be confused with the brown-black gingival melanin pigmentation—diffuse or speckled—common in non-Whites, blue-black embedded fragments of dental amalgam, or other systemic disorders associated with general pigmentation (neurofibromatosis, familial polyposis, Addison disease). Intraoral melanoma is extremely rare and carries a dismal prognosis.

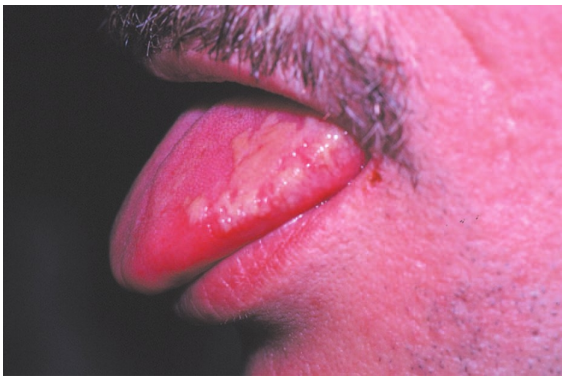
Any area of erythroplakia, enlarging area of leukoplakia, or a lesion that has submucosal depth on palpation should have an incisional biopsy or an exfoliative cytologic examination. Ulcerative lesions are particularly suspicious and worrisome. Specialty referral should be sought early both for diagnosis and treatment. A systematic intraoral examination—including the lateral tongue, floor of the mouth, gingiva, buccal area, palate, and tonsillar fossae—and palpation of the neck for enlarged lymph nodes should be part of any general physical examination, especially in patients over the age of 45 who smoke tobacco or drink immoderately. Indirect or fiberoptic examination of the nasopharynx, oropharynx, hypopharynx, and larynx by an otolaryngologist, head and neck surgeon, or radiation oncologist should also be considered for such patients when there is unexplained or persistent throat or ear pain, oral or nasal bleeding, or oral erythroplakia. Fine-needle

aspiration (FNA) biopsy may expedite the diagnosis if an enlarged lymph node is found.

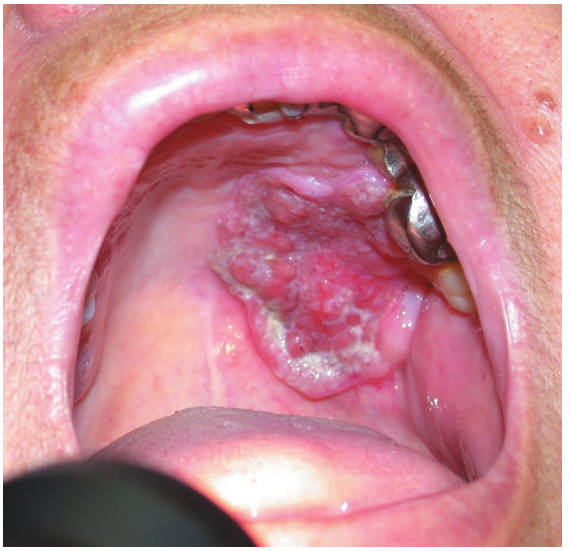
To date, there remain no approved therapies for reversing or stabilizing leukoplakia or erythroplakia. Clinical trials have suggested a role for beta-carotene, celecoxib, vitamin E, and retinoids in producing regression of leukoplakia and reducing the incidence of recurrent squamous cell carcinomas. None have demonstrated benefit in large studies and these agents are not in general use today. The mainstays of management are surveillance following elimination of carcinogenic irritants (eg, smoking tobacco, chewing tobacco or betel nut, drinking alcohol) along with serial biopsies and excisions.

Oral lichen planus is a relatively common (0.5–2% of the population) chronic inflammatory autoimmune disease that may be difficult to diagnose clinically because of its numerous distinct phenotypic subtypes. For example, the reticular pattern may mimic candidiasis or hyperkeratosis, while the erosive pattern may mimic squamous cell carcinoma. Management begins with distinguishing it from other oral lesions. Exfoliative cytology or a small incisional or excisional biopsy is indicated, especially if squamous cell carcinoma is suspected. Therapy of lichen planus is aimed at managing pain and discomfort. Daily topical corticosteroid remains the most effective treatment for symptomatic lichen planus, but cyclosporines, retinoids, and tacrolimus have also been used. Many experts think there is a low rate (1%) of squamous cell carcinoma arising within lichen planus (in addition to the possibility of clinical misdiagnosis) and prevention of malignant transformation remains a goal of treatment.

Hairy leukoplakia occurs on the lateral border of the tongue and is a common early finding in HIV infection (see Chapter 31). It often develops quickly and appears as slightly raised leukoplakic areas with a corrugated or "hairy" surface (Figure 8–6). While much more prevalent in HIV-positive patients, hairy leukoplakia can occur following solid organ transplantation and is associated with Epstein-Barr virus infection and long-term systemic corticosteroid use. Hairy leukoplakia waxes and wanes over time with generally modest irritative symptoms. Acyclovir, valacyclovir, and famciclovir have all been used for treatment but produce only temporary resolution of the condition. It does not appear to predispose to malignant transformation.



▲ **Figure 8–6.** Oral hairy leukoplakia on the side of the tongue in AIDS. (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)



▲ **Figure 8–7.** Squamous cell carcinoma of the palate. (Used, with permission, from Frank Miller, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Oral cavity squamous cell carcinoma can be hard to distinguish from other oral lesions, but early detection is the key to successful management (Figure 8–7). Raised, firm, white lesions with ulcers at the base are highly suspicious and generally quite painful on even gentle palpation. Lesions less than 4 mm in depth have a low propensity to metastasize. Most patients in whom the tumor is detected before it is 2 cm in diameter are cured by local resection. Radiation is reserved for patients with positive margins or metastatic disease. Large tumors are usually treated with a combination of resection, neck dissection, and external beam radiation. Reconstruction, if required, is done at the time of resection and can involve the use of myocutaneous flaps or vascularized free flaps with or without bone. Novel fluorescence-guided surgeries are being developed to improve detection of margins and decrease recurrence.

Oropharyngeal squamous cell carcinoma generally presents later than oral cavity squamous cell carcinoma. The lesions tend to be larger and are often buried within the lymphoid tissue of the palatine or lingual tonsils. Most patients note only unilateral odynophagia and weight loss, but ipsilateral cervical lymphadenopathy is often identified by the careful clinician. While these tumors are typically associated with known carcinogens such as tobacco and alcohol, their epidemiology has changed dramatically over the past 20 years. Despite demonstrated reductions in tobacco and alcohol use within developed nations, the incidence of oropharyngeal squamous cell carcinoma has not declined over this period. Known as a possible cause of head and neck cancer since 1983, **HPV—most commonly,**

type 16—is believed to be the cause of up to 70% of all oropharyngeal squamous cell carcinoma. HPV-positive tumors are readily distinguished by immunostaining of primary tumor or FNA biopsy specimens for the p16 protein, a tumor suppressor protein that is highly correlated with the presence of HPV. These tumors often present in advanced stages of the disease with regional cervical lymph node metastases (stages III and IV), but have a better prognosis than similarly staged lesions in tobacco and alcohol users. This difference in disease control is so apparent in multicenter studies that, based on the presence or absence of the p16 protein, two distinct staging systems for oropharyngeal squamous cell carcinoma were introduced in 2018.

Machiels JP et al. Pembrolizumab given concomitantly with chemoradiation and as maintenance therapy for locally advanced head and neck squamous cell carcinoma: KEYNOTE-412. Future Oncol. 2020;16:1235. [PMID: 32490686]

ORAL CANDIDIASIS

ESSENTIALS OF DIAGNOSIS

- Fluctuating throat or mouth discomfort.
- Associated with systemic or local immunosuppression, such as recent corticosteroid, chemotherapy, or antibiotic use.
- Erythema of the oral cavity or oropharynx with creamy-white, curd-like patches.
- Rapid resolution of symptoms with appropriate treatment.

Clinical Findings

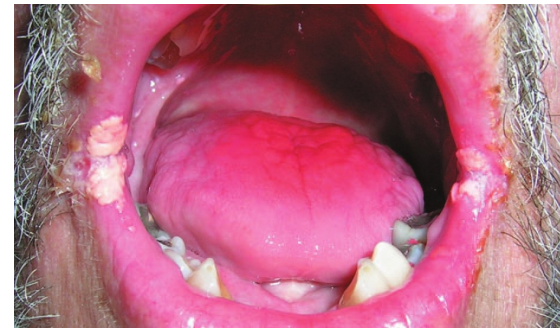
A. Symptoms and Signs

Oral candidiasis (thrush) is usually painful and looks like creamy-white curd-like patches overlying erythematous mucosa (see Figure 6–11). Because these white areas are easily rubbed off (eg, by a tongue depressor)—unlike leukoplakia or lichen planus—only the underlying irregular erythema may be seen. Oral candidiasis is commonly associated with the following risk factors: (1) use of dentures, (2) debilitated state with poor oral hygiene, (3) diabetes mellitus, (4) anemia, (5) chemotherapy or local irradiation, (6) corticosteroid use (oral or systemic), or (7) broad-spectrum antibiotics. Another manifestation of candidiasis is angular cheilitis (also seen in nutritional deficiencies) (Figure 8–8).

B. Diagnostic Studies

The diagnosis is made clinically. A wet preparation using potassium hydroxide will reveal spores and may show nonseptate mycelia. Biopsy will show intraepithelial pseudomycelia of *Candida albicans*.

Candidiasis is often the first manifestation of HIV infection, and HIV testing should be considered in patients with no known predisposing cause for *Candida* overgrowth (see also Chapter 31). The US Department of Health Services Clinical Practice Guideline for Evaluation and Management of Early HIV Infection recommends examination of the oral mucosa with each clinician visit as well as at a dental examination every 6 months for individuals living with HIV.



▲ **Figure 8–8. Severe angular cheilitis in HIV-positive man with oral thrush.** (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Treatment

Effective antifungal therapy may be achieved with any of the following: fluconazole (100 mg orally daily for 7 days), ketoconazole (200–400 mg orally with breakfast [requires acidic gastric environment for absorption] for 7–14 days), clotrimazole troches (10 mg dissolved orally five times daily), or nystatin mouth rinses (500,000 units [5 mL of 100,000 units/mL] held in the mouth before swallowing three times daily). In patients with HIV infection, however, longer courses of therapy with fluconazole may be needed, and oral itraconazole (200 mg/day) may be indicated in fluconazole-refractory cases. Many of the *Candida* species in these patients are resistant to first-line azoles and may require newer medications, such as voriconazole. In addition, 0.12% chlorhexidine or half-strength hydrogen peroxide mouth rinses may provide local relief. Nystatin powder (100,000 units/g) applied to dentures three or four times daily and rinsed off for several weeks may help denture wearers.

Fang J et al. Efficacy of antifungal drugs in the treatment of oral candidiasis: a Bayesian network meta-analysis. J Prosthet Dent. 2020:S0022-3913(20)30076. [PMID: 32165010]
Vila T et al. Oral candidiasis: a disease of opportunity. J Fungi (Basel). 2020;16;6:15. [PMID: 31963180]

GLOSSITIS, GLOSSODYNIA, & BURNING MOUTH SYNDROME

Inflammation of the tongue with loss of filiform papillae leads to a red, smooth-surfaced tongue (**glossitis**). Rarely painful, it may be secondary to nutritional deficiencies (eg, niacin, riboflavin, iron, or vitamin E), drug reactions, dehydration, irritants, or foods and liquids, and possibly to

autoimmune reactions or psoriasis. If the primary cause cannot be identified and corrected, empiric nutritional replacement therapy may be of value.

Glossodynia is burning and pain of the tongue, which may occur with or without glossitis. In the absence of any clinical findings, it has been termed "burning mouth syndrome." Glossodynia with glossitis has been associated with diabetes mellitus, medications (eg, diuretics), tobacco, xerostomia, and candidiasis as well as the listed causes of glossitis. The burning mouth syndrome typically has no identifiable associated risk factors and seems to be most common in postmenopausal women. Treating possible underlying causes, changing long-term medications to alternative ones, and smoking cessation may resolve symptoms of glossitis. Effective treatments for the burning mouth syndrome include alpha-lipoic acid and clonazepam. Clonazepam is most effective as a rapid-dissolving tablet placed on the tongue in doses from 0.25 mg to 0.5 mg every 8–12 hours. Both glossodynia and the burning mouth syndrome are benign, and reassurance that there is no infection or tumor is likely to be appreciated. Unilateral symptoms, symptoms that cannot be related to a specific medication, and symptoms and signs involving regions supplied by other cranial nerves all may suggest neuropathology, and imaging of the brain, brainstem, and skull base with MRI should be considered.

Adamo D et al. Vortioxetine versus other antidepressants in the treatment of burning mouth syndrome: an open-label randomized trial. Oral Dis. 2021;27:1022. [PMID: 32790904]

INTRAORAL ULCERATIVE LESIONS

1. Necrotizing Ulcerative Gingivitis (Trench Mouth, Vincent Angina)

Necrotizing ulcerative gingivitis, often caused by an infection with both spirochetes and fusiform bacilli, is common in young adults under stress (classically in students at examination time). Underlying systemic diseases may also predispose to this disorder. Clinically, there is painful acute gingival inflammation and necrosis, often with bleeding, halitosis, fever, and cervical lymphadenopathy. Warm half-strength peroxide rinses and oral penicillin (250 mg three times daily for 10 days) may help. Dental gingival curettage may prove necessary.

Reddy R et al. Seventeen new cases of chronic ulcerative stomatitis with literature review. Head Neck Pathol. 2019;13:386. [PMID: 30374883]

2. Aphthous Ulcer (Canker Sore, Ulcerative Stomatitis)

Aphthous ulcers are very common and easy to recognize. Their cause remains uncertain, although an association with human herpesvirus 6 has been suggested. Found on freely moving, nonkeratinized mucosa (eg, buccal and labial mucosa and not attached gingiva or palate), they may be single or multiple, are usually recurrent, and appear as painful small round ulcerations with yellow-gray fibrinoid centers surrounded by red halos. Minor aphthous ulcers are less than 1 cm in diameter and generally heal in 10–14 days. Major aphthous ulcers are greater than 1 cm in diameter and can be disabling due to the degree of associated oral pain. Stress seems to be a major predisposing factor to the eruptions of aphthous ulcers.

Treatment is challenging because no single systemic treatment has proven effective. Avoiding local irritants, such as certain toothpastes, may decrease symptoms and episodes. Topical corticosteroids (triamcinolone acetonide, 0.1%, or fluocinonide ointment, 0.05%) in an adhesive base (Orabase Plain) do appear to provide symptomatic relief in many patients. Other topical therapies shown to be effective in controlled studies include diclofenac 3% in hyaluronan 2.5%, doxymycine-cyanoacrylate, mouthwashes containing the enzymes amyloglucosidase and glucose oxidase, and amlexanox 5% oral paste. A 1-week tapering course of prednisone (40–60 mg/day) has also been used successfully. Cimetidine maintenance therapy may be useful in patients with recurrent aphthous ulcers. Thalidomide has been used selectively in recurrent aphthous ulcerations in HIV-positive patients.

Large or persistent areas of ulcerative stomatitis may be secondary to erythema multiforme or drug allergies, acute herpes simplex, pemphigus, pemphigoid, epidermolysis bullosa acquisita, bullous lichen planus, Behçet disease, or IBD. Squamous cell carcinoma may occasionally present in this fashion. When the diagnosis is not clear, incisional biopsy is indicated.

Chaitanya N et al. Efficacy of improvised topical zinc (1%) orabase on oral mucositis during cancer chemo-radiation—a randomized study. J Nutr Sci Vitaminol (Tokyo). 2020;66:93. [PMID: 32350185]

3. Herpes Stomatitis

Herpes gingivostomatitis is common, mild, and short-lived. Clinically, there is initial burning, followed by typical small vesicles that rupture and form scabs. Lesions are most commonly found on the attached gingiva and mucocutaneous junction of the lip, but lesions can also form on the tongue, buccal mucosa, and soft palate. In most adults, it requires no intervention. In immunocompromised persons, however, reactivation of herpes simplex virus infection is frequent and may be severe. Acyclovir (200–800 mg orally five times daily for 7–10 days) or valacyclovir (1000 mg orally twice daily for 7–10 days) may shorten the course and reduce postherpetic pain. These treatments may be effective only when started within 24–48 hours of the onset of initial symptoms (pain, itching, burning) and are not effective once vesicles have erupted. Differential diagnosis includes aphthous stomatitis, erythema multiforme, syphilitic chancre, and carcinoma.

Mazzarello V et al. Do sunscreens prevent recurrent herpes labialis in summer? J Dermatolog Treat. 2019;30:179. [PMID: 29804485]

Petti S et al. The controversial natural history of oral herpes simplex virus type 1 infection. Oral Dis. 2019;25:1850. [PMID: 31733122]

PHARYNGITIS & TONSILLITIS

ESSENTIALS OF DIAGNOSIS

- Centor criteria for streptococcal pharyngitis: exudate or swelling on tonsils, anterior cervical adenopathy, fever, lack of cough.
- Goal is to treat group A beta-hemolytic streptococcal infection to prevent subsequent rheumatic fever (rash, arthralgias, myocardtis) and other sequelae (glomerulonephritis, posterior pharyngeal abscess).

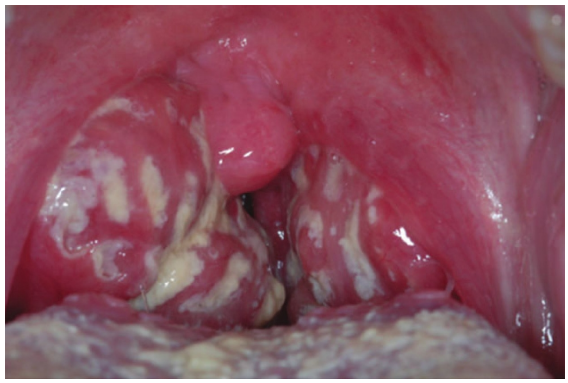
General Considerations

Pharyngitis and tonsillitis account for over 10% of all office visits to primary care clinicians and 50% of outpatient antibiotic use. The main concern is determining who is likely to have a group A beta-hemolytic streptococcal (GABHS) infection, since this can lead to subsequent complications, such as rheumatic fever and glomerulonephritis. A second public health policy concern is reducing the extraordinary cost (both in dollars and in the development of antibiotic-resistant *S pneumoniae*) in the United States associated with unnecessary antibiotic use. Numerous well-done studies and experience with rapid laboratory tests for detection of streptococci (eliminating the delay caused by culturing) have informed a consensus recommendation.

Clinical Findings

A. Symptoms and Signs

The clinical features most suggestive of GABHS pharyngitis include fever over 38°C, tender anterior cervical adenopathy, lack of a cough, and pharyngotonsillar exudate (Figure 8–9). These four features (**the Centor criteria**), when present, strongly suggest GABHS. When two or three of the four are present, there is an intermediate likelihood of GABHS. When only one criterion is present, GABHS is unlikely. Sore throat may be severe, with odynophagia, tender adenopathy, and a scarlatiniform rash. An elevated white count and left shift are also possible. Hoarseness, cough, and coryza are not suggestive of this disease. It is also rare to have GABHS in individuals younger than 3 years old.



▲ **Figure 8–9.** Marked exudative pharyngitis and tonsillitis due to group A beta-hemolytic streptococci. (Used, with permission, from Lawrence B. Stack, MD, in Knoop KJ, Stack LB, Storrow AB, Thurman RJ. *The Atlas of Emergency Medicine*, 5th ed. McGraw Hill, 2021.)

Marked lymphadenopathy and a shaggy, white-purple tonsillar exudate, often extending into the nasopharynx, suggest mononucleosis, especially if present in a young adult. With about 90% sensitivity, lymphocyte-to-white-blood-cell ratios of greater than 35% suggest EBV infection and not tonsillitis. Hepatosplenomegaly and a positive heterophile agglutination test or elevated anti-EBV titer are corroborative. However, about one-third of patients with infectious mononucleosis have secondary streptococcal tonsillitis, requiring treatment. Ampicillin should routinely be avoided if mononucleosis is suspected because it induces a rash that might be misinterpreted by the patient as a penicillin allergy. Diphtheria (extremely rare but described in persons with alcohol use disorder) presents with low-grade fever and an ill patient with a gray tonsillar pseudomembrane.

The most common pathogens other than GABHS in the differential diagnosis of "sore throat" are viruses, *Neisseria gonorrhoeae, Mycoplasma,* and *Chlamydia trachomatis.* Rhinorrhea and lack of exudate would suggest a virus, but in practice it is not possible to confidently distinguish viral upper respiratory infection from GABHS on clinical grounds alone. Infections with *Corynebacterium diphtheria,* anaerobic streptococci, and *Corynebacterium haemolyticum* (which responds better to erythromycin than penicillin) may also mimic pharyngitis due to GABHS.

B. Laboratory Findings

A single-swab throat culture is 90–95% sensitive and the rapid antigen detection testing (RADT) is 90–99% sensitive for GABHS. Results from the RADT are available in about 15 minutes.

Treatment

The Infectious Diseases Society of America recommends laboratory confirmation of the clinical diagnosis by means of either throat culture or RADT of the throat swab. The American College of Physicians–American Society of Internal Medicine (ACP-ASIM), in collaboration with the CDC, advocates use of a clinical algorithm alone—in lieu of microbiologic testing—for confirmation of the diagnosis in adults for whom the suspicion of streptococcal infection is high. Others examine the assumptions of the ACP-ASIM guideline for using a clinical algorithm alone and question whether those recommendations will achieve the stated objective of dramatically decreasing excess antibiotic use. A reasonable strategy to follow is that patients with zero or one Centor criteria are at very low risk for GABHS and therefore do not need throat cultures or RADT of the throat swab and should not receive antibiotics. Patients with two or three Centor criteria need throat cultures or RADT of the throat swab, since positive results would warrant antibiotic treatment. Patients who have all four Centor

criteria are likely to have GABHS and can receive empiric therapy without throat culture or RADT.

Oral antibiotics are the preferred first-line therapy. Penicillin V potassium (250 mg orally three times daily or 500 mg twice daily for 10 days) or cefuroxime axetil (250 mg orally twice daily for 5–10 days) are both effective. The efficacy of a 5-day regimen of penicillin V potassium appears to be similar to that of a 10-day course, with a 94% clinical response rate and an 84% streptococcal eradication rate. Erythromycin (also active against *Mycoplasma* and *Chlamydia*) is a reasonable alternative to penicillin in allergic patients. Cephalosporins are somewhat more effective than penicillin in producing bacteriologic cures; 5-day courses of cefpodoxime and cefuroxime have been successful. The macrolide antibiotics have also been reported to be successful in shorter-duration regimens. Azithromycin (500 mg once daily), because of its long half-life, needs to be taken for only 3 days. For patients in whom medication compliance is in question, or those unable to take oral medication, a single intramuscular injection of benzathine penicillin or procaine penicillin, 1.2 million units is an effective alternative.

Adequate antibiotic treatment usually avoids the streptococcal complications of scarlet fever, rheumatic myocarditis, glomerulonephritis, and local abscess formation.

Antibiotics for treatment failures are also somewhat controversial. Surprisingly, penicillin-tolerant strains are not isolated more frequently in those who fail treatment than in those treated successfully with penicillin. The reasons for failure appear to be complex, and a second course of treatment with the same medication is reasonable. Alternatives to penicillin include cefuroxime and other cephalosporins, dicloxacillin (which is beta-lactamase–resistant), and amoxicillin with clavulanate. When there is a history of penicillin allergy, alternatives should be used, such as erythromycin. Erythromycin resistance—with failure rates of about 25%—is an increasing problem in many areas. In cases of severe penicillin allergy, cephalosporins should be avoided since cross-reaction occurs in greater than 8% of cases.

Ancillary treatment of pharyngitis includes analgesics and anti-inflammatory agents, such as aspirin, acetaminophen, and corticosteroids. In meta-analysis, corticosteroids increased the likelihood of complete pain resolution at 24 hours by threefold without an increase in recurrence or adverse events. Some patients find that salt water gargling is soothing. In severe cases, anesthetic gargles and lozenges (eg, benzocaine) may provide additional symptomatic relief. Occasionally, odynophagia is so intense that hospitalization for intravenous hydration and antibiotics is necessary. (See Chapter 33.)

Patients who have had rheumatic fever should be treated with a continuous course of antimicrobial prophylaxis (penicillin G, 500 mg once daily orally, or erythromycin, 250 mg twice daily orally) for at least 5 years.

Cohen JF et al. Efficacy and safety of rapid tests to guide antibiotic prescriptions for sore throat. Cochrane Database Syst Rev. 2020;6:CD012431. [PMID: 32497279]

Klein MR. Infections of the oropharynx. Emerg Med Clin North Am. 2019;37:69. [PMID: 30454781]

Sykes EA et al. Pharyngitis: approach to diagnosis and treatment. Can Fam Physician. 2020;66:251. [PMID: 32273409]

PERITONSILLAR ABSCESS & CELLULITIS

When infection penetrates the tonsillar capsule and involves the surrounding tissues, peritonsillar cellulitis results. Following therapy, peritonsillar cellulitis usually either resolves over several days or evolves into peritonsillar abscess. Peritonsillar abscess (**quinsy**) and cellulitis present with severe sore throat, odynophagia, trismus, medial deviation of the soft palate and peritonsillar fold, and an abnormal muffled ("hot potato") voice. CT may be a useful adjunct to clinical suspicion, but imaging is not required for the diagnosis. The existence of an abscess may be confirmed by aspirating pus from the peritonsillar fold just superior and medial to the upper pole of the tonsil. A 19-gauge or 21-gauge needle should be passed medial to the molar and no deeper than 1 cm, because the internal carotid artery may lie more medially than its usual location and pass posterior and deep to the tonsillar fossa. Most commonly, patients with peritonsillar abscess present to the emergency department and receive a dose of parenteral amoxicillin (1 g), amoxicillin-sulbactam (3 g), or clindamycin (600–900 mg). Less severe cases and patients who are able to tolerate oral intake may be treated for 7–10 days with oral antibiotics, including amoxicillin, 500 mg three times a day; amoxicillin-clavulanate, 875 mg twice a day; or clindamycin, 300 mg four times daily.

Although antibiotic treatment is generally undisputed, there is controversy regarding the surgical management of peritonsillar abscess. Methods include needle aspiration, incision and drainage, and tonsillectomy. Some clinicians incise and drain the area and continue with parenteral antibiotics, whereas others aspirate only and monitor as an outpatient. The data are largely equivocal for all three approaches. In patients with more severe or recurrent peritonsillar abscesses, it may be appropriate to consider immediate tonsillectomy (quinsy tonsillectomy) in the acutely infected setting, although practitioners have moved away from this approach because of the potential for complications.

About 10% of patients with peritonsillar abscess exhibit relative indications for tonsillectomy after the infection as resolved. All three approaches are effective. Regardless of the method used, one must be sure the abscess is adequately treated, since complications such as extension to the retropharyngeal, deep neck, and posterior mediastinal spaces are possible. Bacteria may also be aspirated into the lungs, resulting in pneumonia. There is controversy about whether a single abscess is a sufficient indication for tonsillectomy; about 30% of patients aged 17–30 who do not undergo early planned tonsillectomy following peritonsillar abscess ultimately undergo surgery, and only about 13% of those over 30 have their tonsils removed. Recurrent or atypical peritonsillar abscesses in older adults should also be evaluated for an underlying head and neck malignancy.

Klug TE et al. Complications of peritonsillar abscess. Ann Clin Microbiol Antimicrob. 2020;19:32. [PMID: 32731900]

Luo MS et al. Needle aspiration versus incision and drainage under local anaesthesia for the treatment of peritonsillar abscess. Eur Arch Otorhinolaryngol. 2020;277:645. [PMID: 31555918]

DEEP NECK INFECTIONS

ESSENTIALS OF DIAGNOSIS

- Marked acute neck pain and swelling.
- Abscesses are emergencies because rapid airway compromise may occur.
- May spread to the mediastinum or cause sepsis.

General Considerations

Deep neck abscesses most commonly originate from odontogenic infections. Other causes include suppurative lymphadenitis; direct spread of pharyngeal infection; penetrating trauma; pharyngoesophageal foreign bodies; cervical osteomyelitis; and intravenous injection of the internal jugular vein, especially in people with substance use disorders. **Ludwig angina** is the most commonly encountered neck space infection. It is a cellulitis of the sublingual and submaxillary spaces, often arising from infection of the mandibular dentition. **Ludwig angina is an emergency** as it may cause rapid upper airway compromise and necessitate creation of a surgical airway. Recurrent deep neck infection may suggest an underlying congenital lesion, such as a branchial cleft cyst. Suppurative lymphadenopathy in middle-aged persons who smoke cigarettes and drink alcohol regularly should be considered a manifestation of malignancy (typically metastatic squamous cell carcinoma) until proven otherwise.

Clinical Findings

Patients with Ludwig angina have edema and erythema of the upper neck under the chin and often of the floor of the mouth. The tongue may be displaced upward and backward by the posterior spread of cellulitis, and coalescence of pus is often present in the floor of mouth. This may lead to occlusion of the airway. Microbiologic isolates include streptococci, staphylococci, *Bacteroides,* and *Fusobacterium*. Patients with diabetes may have different flora, including *Klebsiella*, and a more aggressive clinical course.

Patients with deep neck abscesses usually present with marked neck pain and swelling. Fever is common but not always present. **Deep neck abscesses are emergencies because they may rapidly compromise the airway.** Untreated or inadequately treated, they may spread to the mediastinum or cause sepsis.

Contrast-enhanced CT usually augments the clinical examination in defining the extent of the infection. It often will distinguish inflammation and phlegmon (requiring antibiotics) from abscess (requiring drainage) and define for the surgeon the extent of an abscess. CT with MRI may also identify thrombophlebitis of the internal jugular vein secondary to oropharyngeal inflammation. This condition, known as **Lemierre syndrome**, is rare and usually associated with severe headache. The presence of pulmonary infiltrates consistent with septic emboli in the setting of a neck abscess should lead one to suspect Lemierre syndrome or injection drug use, or both.

Treatment

Usual doses of penicillin plus metronidazole, ampicillin-sulbactam, clindamycin, or selective cephalosporins are good initial choices for treatment of Ludwig angina. Culture and sensitivity data are then used to refine the choice. Dental consultation is advisable to address the offending tooth or teeth. External drainage via bilateral submental incisions is required if the airway is threatened or when medical therapy has not reversed the process.

Treatment of deep neck abscesses includes securing the airway, intravenous antibiotics, and incision and drainage. When the infection involves the floor of the mouth, base of the tongue, or the supraglottic or paraglottic space, the airway may be secured either by intubation or tracheotomy. Tracheotomy is preferable in the patients with substantial pharyngeal edema, since attempts at intubation may precipitate acute airway obstruction. Bleeding in association with a deep neck abscess is very rare but suggests carotid artery or internal jugular vein involvement and requires prompt neck exploration both for drainage of pus and for vascular control.

Patients with Lemierre syndrome require prompt institution of antibiotics appropriate for *Fusobacterium necrophorum* as well as the more usual upper airway pathogens. The use of anticoagulation in treatment is of no proven benefit.

Fiorella ML et al. New laboratory predictive tools in deep neck space infections. Acta Otorhinolaryngol Ital. 2020;40:332. [PMID: 3329922]
Lee WS et al. Lemierre's syndrome: a forgotten and re-emerging infection. J Microbiol Immunol Infect. 2020;53:513. [PMID: 32303484]
Li RM et al. Infections of the neck. Emerg Med Clin North Am. 2019;37:95. [PMID: 30454783]
Velhonoja J et al. Deep neck space infections: an upward trend and changing characteristics. Eur Arch Otorhinolaryngol. 2020;277:863. [PMID: 31797041]

SNORING

ESSENTIALS OF DIAGNOSIS

- Noise produced on inspiration due to upper aerodigestive tract blockage during sleep.
- Snoring is associated with obstructive sleep apnea (OSA) but may not alone disrupt sleep quality.

General Considerations

Ventilation disorders during sleep are extremely common. While OSA occurs in 5–10% of Americans, clinically

relevant snoring may occur in as many as 59%. In general, sleep-disordered breathing problems are attributed to narrowing of the upper aerodigestive tract during sleep due to changes in position, muscle tone, and soft tissue hypertrophy or laxity. The most common sites of obstruction are the oropharynx and the base of the tongue. The spectrum of the problem ranges from simple snoring without cessation of airflow to OSA with long periods of apnea and life-threatening physiologic sequelae. OSA is discussed in Chapter 9. In contrast to OSA, snoring is almost exclusively a social problem, and despite its prevalence and association with OSA, there is comparatively little known about the management of this problem.

Clinical Findings

A. Symptoms and Signs

All patients who complain of snoring should be evaluated for OSA as discussed in Chapter 9. Symptoms of OSA (including snoring, excessive daytime somnolence, daytime headaches, and weight gain) may be present in as many as 30% of patients without demonstrable apnea or hypopnea on formal testing. Clinical examination should include examination of the nasal cavity, nasopharynx, oropharynx, and larynx to help exclude other causes of dynamic airway obstruction. In many cases of isolated snoring, the palate and uvula appear enlarged and elongated with excessive mucosa hanging below the muscular portion of the soft palate.

B. Imaging and Diagnostic Testing

Sleep examination with polysomnography is strongly advised in the evaluation of a patient with complaints of snoring. Radiographic imaging of the head or neck is generally not necessary. Additional testing may include sleep endoscopy.

Treatment

Expeditious and inexpensive management solutions of snoring are sought, often with little or no benefit. Diet modification and physical exercise can lead to improvement in snoring through the weight loss and improvement in pharyngeal tone that accompanies overall physical conditioning. Position change during sleep can be effective, and time-honored treatments, such as placing a golf or tennis ball into a pocket sewn on the back of the pajama top worn during sleep, may satisfactorily eliminate symptoms by ensuring recumbency on one side. Although numerous pharmacologic therapies have been endorsed, none demonstrate any significant utility when scrutinized.

Anatomic management of snoring can be challenging. As with OSA, snoring can come from a number of sites in the upper aerodigestive tract. While medical or surgical correction of nasal obstruction may help alleviate snoring problems, most interventions aim to improve airflow through the nasopharynx and oropharynx. Nonsurgical options include mandibular advancement appliances designed to pull the base of the tongue forward and continuous positive airway pressure via face or nasal mask. Compliance with both of these treatment options is problematic because snorers without OSA do not notice the physiologic benefits of these devices noted by patients with sleep apnea.

Surgical correction of snoring is most commonly directed at the soft palate. Historical approaches involved resection of redundant mucosa and the uvula similar to uvulopalatopharyngoplasty that is used for OSA. Regardless of how limited the procedure or what technique was used, the postoperative pain, expense of general anesthesia, and high recurrence rates limit the utility of these procedures. Office-based approaches are more widely used because of these limitations. Most of these procedures aim to stiffen the palate to prevent vibration rather than remove it. A series of procedures, including injection snoreplasty, radiofrequency thermal fibrosis, and an implantable palatal device, have been used with variable success and patient tolerance. The techniques can be technically challenging. Persistent symptoms may occur following initial treatment necessitating costly (and sometimes painful) repeat procedures. The durability of these procedures in alleviating symptoms is also poorly understood, and late failures can lead to patient and clinician frustration.

Suzuki M et al. Effect of position therapy and oral devices on sleep parameters in patients with obstructive sleep apnea. Eur Arch Otorhinolaryngol. 2021;278:4545. [PMID: 33864481]

DISEASES OF THE SALIVARY GLANDS

ACUTE INFLAMMATORY SALIVARY GLAND DISORDERS

1. Sialadenitis

Acute bacterial sialadenitis most commonly affects either the parotid or submandibular gland. It typically presents with acute swelling of the gland, increased pain and swelling with meals, and tenderness and erythema of the duct opening. Pus often can be massaged from the duct. Sialadenitis often occurs in the setting of dehydration or in association with chronic illness. Underlying Sjögren syndrome and chronic periodontitis may contribute. Ductal obstruction, often by an inspissated mucous plug, is followed by salivary stasis and secondary infection. The most common organism recovered from purulent draining saliva is *S aureus*. Treatment consists of intravenous antibiotics, such as nafcillin (1 g intravenously every 4–6 hours), and measures to increase salivary flow, including hydration, warm compresses, sialagogues (eg, lemon drops), and massage of the gland. Treatment can usually then be switched to an oral agent based on clinical improvement and microbiologic results to complete a 10-day treatment course. Less severe cases can often be treated with oral antibiotics with similar spectrum. Complete resolution of parotid swelling and pain can take 2–3 weeks. Failure of the process to improve and ultimately resolve on this regimen suggests abscess formation, ductal stricture, stone, or tumor causing obstruction. Ultrasound or CT scan may be helpful in

establishing the diagnosis. In the setting of acute illness, a severe and potentially life-threatening form of sialadenitis, sometimes called suppurative sialadenitis, may develop. The causative organism is usually *S aureus*, but often no pus will drain from Stensen papilla. These patients often do not respond to rehydration and intravenous antibiotics and thus may require operative incision and drainage to resolve the infection. In patients with bilateral parotid sialadenitis, mumps should be considered.

2. Sialolithiasis

Calculus formation is more common in the Wharton duct (draining the submandibular glands) than in the Stensen duct (draining the parotid glands). Clinically, a patient may note postprandial pain and local swelling, often with a history of recurrent acute sialadenitis. Stones in the Wharton duct are usually large and radiopaque, whereas those in the Stensen duct are usually radiolucent and smaller. Those very close to the orifice of the Wharton duct may be palpated manually in the anterior floor of the mouth and removed intraorally by dilating or incising the distal duct. Those more than 1.5–2 cm from the duct are too close to the lingual nerve to be removed safely in this manner. Similarly, dilation of the Stensen duct, located on the buccal surface opposite the second maxillary molar, may relieve distal stricture or allow a small stone to pass. Sialoendoscopy for the management of chronic sialolithiasis is superior to extracorporeal shock-wave lithotripsy and fluoroscopically guided basket retrieval. Repeated episodes of sialadenitis are usually associated with stricture and chronic infection. If the obstruction cannot be safely removed or dilated, excision of the gland may be necessary to relieve recurrent symptoms.

Ferneini EM. Managing sialolithiasis. J Oral Maxillofac Surg. 2021;79:1581. [PMID: 34215413]

CHRONIC INFLAMMATORY & INFILTRATIVE DISORDERS OF THE SALIVARY GLANDS

Numerous infiltrative disorders may cause unilateral or bilateral parotid gland enlargement. Sjögren syndrome and sarcoidosis are examples of lymphoepithelial and granulomatous diseases that may affect the salivary glands. Metabolic disorders, including alcoholism, diabetes mellitus, and vitamin deficiencies, may also cause diffuse enlargement. Several medications have been associated with parotid enlargement, including thioureas, iodine, and medications with cholinergic effects (eg, phenothiazines), which stimulate salivary flow and cause more viscous saliva.

SALIVARY GLAND TUMORS

A general rule of thumb is that the smaller the size of the salivary gland with a present mass, the more likely the possibility of malignancy. Approximately 80% of salivary gland tumors occur in the parotid gland. In adults, about 80% of these are benign. In the submandibular triangle, it is sometimes difficult to distinguish a primary submandibular gland tumor from a metastatic submandibular space node. Only 50–60% of primary submandibular tumors are benign. Tumors of the minor salivary glands are most likely to be malignant, with adenoid cystic carcinoma predominating, and may be found throughout the oral cavity or oropharynx.

Most parotid tumors present as an asymptomatic mass in the superficial part of the gland. Their presence may have been noted by the patient for months or years. Facial nerve involvement correlates strongly with malignancy. Tumors may extend deep to the plane of the facial nerve or may originate in the parapharyngeal space. In such cases, medial deviation of the soft palate is visible on intraoral examination. MRI and CT scans have largely replaced sialography in defining the extent of tumor. At least one study demonstrates the potential benefit of enhanced MRI imaging in distinguishing among Warthin tumors and pleomorphic adenomas and malignant salivary gland tumors.

When the clinician encounters a patient with an otherwise asymptomatic salivary gland mass where tumor is the most likely diagnosis, the choice is whether to simply excise the mass via a parotidectomy with facial nerve dissection or submandibular gland excision or to first obtain an FNA biopsy. Although the accuracy of FNA biopsy for malignancy has been reported to be quite high, results vary among institutions. If a negative FNA biopsy would lead to a decision not to proceed to surgery, then it should be considered. Poor overall health of the patient and the possibility of inflammatory disease as the cause of the mass are situations where FNA biopsy might be helpful. In otherwise straightforward nonrecurrent cases, excision generally is indicated. In benign and small, low-grade malignant tumors, no additional treatment is needed. Postoperative irradiation is indicated for larger and high-grade cancers.

Benchetrit L et al. Major salivary gland cancer with distant metastasis upon presentation: patterns, outcomes, and imaging implications. Otolaryngol Head Neck Surg. 2021 Nov 16. [Epub ahead of print] [PMID: 34784258]

DISEASES OF THE LARYNX

HOARSENESS & STRIDOR

The primary symptoms of laryngeal disease are hoarseness and stridor. Hoarseness is caused by an abnormal vibration of the vocal folds. The voice is breathy when too much air passes incompletely apposed vocal folds, as in unilateral vocal fold paralysis or vocal fold mass. The voice is harsh when the vocal folds are stiff and vibrate irregularly, as is the case in laryngitis or malignancy. Heavy, edematous vocal folds produce a rough, low-pitched vocal quality. Stridor (a high-pitched, typically inspiratory, sound) is the result of turbulent airflow from a narrowed upper airway. Airway narrowing at or above the vocal folds produces inspiratory stridor. Airway narrowing below the vocal fold level produces either expiratory or biphasic stridor. The timing and rapidity of onset of stridor are critically important in determining the seriousness of the airway problem. **All cases of stridor should be evaluated by a specialist and rapid-onset stridor should be evaluated emergently.**

Evaluation of an abnormal voice begins with obtaining a history of the circumstances preceding its onset and an examination of the airway. **All patients with hoarseness that has persisted beyond 2 weeks should be evaluated by an otolaryngologist with laryngoscopy.** Especially when the patient has a history of tobacco use, laryngeal cancer or lung cancer (leading to paralysis of a recurrent laryngeal nerve), or concerns for cough and aspiration, must be strongly considered. In addition to structural causes of dysphonia, laryngoscopy can help identify functional problems with the voice, including vocal fold paralysis, muscle tension dysphonia, and spasmodic dysphonia.

Ross J et al. Utility of audiometry in the evaluation of patients presenting with dysphonia. Ann Otol Rhinol Laryngol. 2020;129:333. [PMID: 31731878]

COMMON LARYNGEAL DISORDERS

1. Acute Laryngitis

Acute laryngitis is probably the most common cause of hoarseness, which may persist for a week or so after other symptoms of an upper respiratory infection have cleared. Supportive care includes resting the voice, drinking enough fluid to stay hydrated, and breathing humidified air. The patient should be warned to avoid vigorous use of the voice (singing, shouting) until their voice returns to normal, since persistent use may lead to the formation of traumatic vocal fold hemorrhage, polyps, and cysts. Although thought to be usually viral in origin, both *M catarrhalis* and *H influenzae* may be isolated from the nasopharynx at higher than expected frequencies. Despite this finding, a meta-analysis has failed to demonstrate any convincing evidence that antibiotics significantly alter the natural resolution of acute laryngitis. Erythromycin may speed improvement of hoarseness at 1 week and cough at 2 weeks when measured subjectively. Oral or intramuscular corticosteroids may be used in highly selected cases of professional vocalists to speed recovery and allow scheduled performances. Examination of the vocal folds and assessment of vocal technique are mandatory prior to corticosteroid initiation, since inflamed vocal folds are at greater risk for hemorrhage and the subsequent development of traumatic vocal fold pathology.

Huang T et al. Efficacy of inhaled budesonide on serum inflammatory factors and quality of life among children with acute infectious laryngitis. Am J Otolaryngol. 2021;42:102820. [PMID: 33188988]

2. Laryngopharyngeal Reflux

ESSENTIALS OF DIAGNOSIS

- Commonly associated with hoarseness, throat irritation, heartburn, foreign body sensation, and chronic cough.
- Symptoms typically occur when upright, and many patients do not experience classic heartburn.
- Laryngoscopy is critical to exclude other causes of hoarseness.
- Diagnosis is often made based on response to PPI therapy.
- Treatment failure with PPIs is common and suggests other etiologies.

Gastroesophageal reflux into the larynx (laryngopharyngeal reflux) is considered a cause of chronic hoarseness when other causes of abnormal vocal fold vibration (such as tumor or nodules) have been excluded by laryngoscopy. GERD has also been suggested as a contributing factor to other symptoms, such as throat clearing, throat discomfort, chronic cough, a sensation of postnasal drip, esophageal spasm, and some cases of asthma. Since less than half of patients with laryngeal acid exposure have typical symptoms of heartburn and regurgitation, the lack of such symptoms should not be construed as eliminating this cause. Indeed, **most patients with symptomatic laryngopharyngeal reflux, as it is now called, do not meet criteria for GERD by pH probe testing** and these entities must be considered separately. The prevalence of this condition is hotly debated in the literature, and laryngopharyngeal reflux may not be as common as once thought.

Evaluation should initially exclude other causes of dysphonia through laryngoscopy; consultation with an otolaryngologist is advisable. Many clinicians opt for an empiric trial of a PPI since no gold standard exists for diagnosing this condition. Such an empiric trial should not precede visualization of the vocal folds to exclude other causes of hoarseness. When used, the American Academy of Otolaryngology–Head and Neck Surgery recommends twice-daily therapy with full-strength PPI (eg, omeprazole 40 mg orally twice daily or equivalent) for a minimum of 3 months. Patients may note improvement in symptoms after 3 months, but the changes in the larynx often take 6 months to resolve. If symptoms improve and cessation of therapy leads to symptoms again, then a PPI is resumed at the lowest dose effective for remission, usually daily but at times on a demand basis. Although H_2-receptor antagonists are an alternative to PPIs, they are generally both less clinically effective and less cost-effective. Nonresponders should undergo pH testing and manometry. Twenty-four-hour pH monitoring of the pharynx should best document laryngopharyngeal reflux and is advocated by some as the initial management step, but it is costly, more difficult, and less available than lower esophageal monitoring alone. Double pH probe (proximal and distal esophageal probes) testing is the best option for evaluation, since lower esophageal pH monitoring alone does not correlate well with laryngopharyngeal reflux symptoms. Oropharyngeal pH probe testing is available, but its ability to predict response to reflux treatment in patients with laryngopharyngeal reflux is not known.

Chae M et al. A prospective randomized clinical trial of combination therapy with proton pump inhibitors and mucolytics in patients with laryngopharyngeal reflux. Ann Otol Rhinol Laryngol. 2020;129:781. [PMID: 32186395]
Lechien JR et al. Laryngopharyngeal reflux: a state-of-the-art algorithm management for primary care physicians. J Clin Med. 2020;9:3618. [PMID: 33182684]

3. Recurrent Respiratory Papillomatosis

Papillomas are common lesions of the larynx and other sites where ciliated and squamous epithelia meet. Unlike oral papillomas, recurrent respiratory papillomatosis typically becomes symptomatic, with hoarseness that occasionally progresses over weeks to months. These papillomas are almost always due to HPV types 6 and 11. Repeated laser vaporizations or cold knife resections via operative laryngoscopy are the mainstay of treatment. Severe cases can cause airway compromise in adults and may require treatment as often as every 6 weeks to maintain airway patency. Extension can occur into the trachea and lungs. Tracheotomy should be avoided, if possible, since it introduces an additional squamociliary junction for which papillomas appear to have an affinity. Interferon treatment has been under investigation for many years but is only indicated in severe cases with pulmonary involvement. Rarely, cases of malignant transformation have been reported (often in smokers), but recurrent respiratory papillomatosis should generally be thought of as a benign condition. Cidofovir (a cytosine nucleotide analog in use to treat cytomegalovirus retinitis) has been used with success as intralesional therapy for recurrent respiratory papillomatosis. Because cidofovir causes adenocarcinomas in laboratory animals, its potential for carcinogenesis is being monitored. The quadrivalent and new 9 serotype recombinant human HPV vaccines (Gardasil and Gardasil 9) offer hope for the eventual prevention of this benign, but terribly morbid, disease.

Allen CT. Biologics for the treatment of recurrent respiratory papillomatosis. Otolaryngol Clin North Am. 2021;54:769. [PMID: 34099306]

4. Epiglottitis

Epiglottitis (or, more correctly, supraglottitis) should be suspected when a patient presents with a rapidly developing sore throat or when odynophagia (pain on swallowing) is out of proportion to apparently minimal oropharyngeal findings on examination. It is more common in diabetic patients and may be viral or bacterial in origin. Rarely in the era of *H influenzae* type b vaccine is this bacterium isolated in adults. Unlike in children, indirect laryngoscopy is generally safe and may demonstrate a swollen, erythematous epiglottis. Lateral plain radiographs may demonstrate an enlarged epiglottis (the epiglottis "thumb sign"). Initial treatment is hospitalization for intravenous antibiotics—eg, ceftizoxime, 1–2 g intravenously every 8–12 hours; or cefuroxime, 750–1500 mg intravenously every 8 hours; and dexamethasone, usually 4–10 mg as initial bolus, then 4 mg intravenously every 6 hours—and observation of the airway. Corticosteroids may be tapered as symptoms and signs resolve. Similarly, substitution of oral antibiotics may be appropriate to complete a 10-day course. Less than 10% of adults require intubation. Indications for intubation are dyspnea, rapid pace of sore throat (where progression to airway compromise may occur before the effects of corticosteroids and antibiotics), and endolaryngeal abscess noted on CT imaging. If the patient is not intubated, prudence suggests monitoring oxygen saturation with continuous pulse oximetry and initial admission to a monitored unit.

Gottlieb M et al. Ultrasound for airway management: an evidence-based review for the emergency clinician. Am J Emerg Med. 2020;38:1007. [PMID: 31843325]
Sideris A et al. A systematic review and meta-analysis of predictors of airway intervention in adult epiglottitis. Laryngoscope. 2020;130:465. [PMID: 31173373]

MASSES OF THE LARYNX

1. Traumatic Lesions of the Vocal Folds

Vocal fold nodules are smooth, paired lesions that form at the junction of the anterior one-third and posterior two-thirds of the vocal folds. They are a common cause of hoarseness resulting from vocal abuse. In adults, they are referred to as "singer's nodules" and in children as "screamer's nodules." Treatment requires modification of voice habits, and referral to a speech therapist is indicated. While nearly all true nodules will resolve with behavior modification, recalcitrant nodules may require surgical excision. Often, additional pathology, such as a polyp or cyst, may be encountered.

Vocal fold polyps are unilateral masses that form within the superficial lamina propria of the vocal fold. They are related to vocal trauma and seem to follow resolution of vocal fold hemorrhage. Small, sessile polyps may resolve with conservative measures, such as voice rest and corticosteroids, but larger polyps are often irreversible and require operative removal to restore normal voice.

Vocal fold cysts are also considered traumatic lesions of the vocal folds and are either true cysts with an epithelial lining or pseudocysts. They typically form from mucus-secreting glands on the inferior aspect of the vocal folds. Cysts may fluctuate in size from week to week and cause a variable degree of hoarseness. They rarely, if ever, resolve completely and may leave behind a sulcus, or vocal fold scar, if they decompress or are marsupialized. Such scarring can be a frustrating cause of permanent dysphonia.

Polypoid corditis is different from vocal fold polyps and may form from loss of elastin fibers and loosening of the intracellular junctions within the lamina propria. This loss allows swelling of the gelatinous matrix of the superficial lamina propria (called **Reinke edema**). These changes in the vocal folds are strongly associated with smoking, but also with vocal abuse, chemical industrial irritants, and hypothyroidism. While this problem is common in both male and female smokers, women seem more troubled by the characteristic decline in modal pitch caused by the increased mass of the vocal folds. If the patient stops smoking or the lesions cause stridor and airway obstruction,

surgical resection of the hyperplastic vocal fold mucosa may be indicated to improve the voice or airway, or both.

A common but often unrecognized cause of hoarseness and odynophonia are **contact ulcers** or their close relatives, **granulomas**. Both lesions form on the vocal processes of the arytenoid cartilages, and patients often can correctly inform the clinician which side is affected. The cause of these ulcers and granulomas is disputed, but they are clearly related to trauma and may be related to exposure of the underlying perichondrium. They are common following intubation and generally resolve quite quickly. Chronic ulceration or granuloma formation has been associated with gastroesophageal reflux but is also common in patients with muscle tension dysphonia. Treatment is often multimodal, and an inhaled corticosteroid (eg, fluticasone 440 mcg twice daily) may be the most effective pharmacologic therapy. Adjunctive treatment measures include PPI therapy (omeprazole 40 mg orally twice daily, or equivalent) and voice therapy with special attention to vocal hygiene. Rare cases can be quite stubborn and persistent without efficacious therapy. Surgical removal is rarely, if ever, required for nonobstructive lesions.

Alegria R et al. Effectiveness of voice therapy in patients with vocal fold nodules: a systematic search and narrative review. Eur Arch Otorhinolaryngol. 2020;277:2951. [PMID: 32444967]

2. Laryngeal Leukoplakia

Leukoplakia of the vocal folds is commonly found in association with hoarseness in smokers. Direct laryngoscopy with biopsy is advised in almost all cases. Histologic examination usually demonstrates mild, moderate, or severe dysplasia. In some cases, invasive squamous cell carcinoma is present in the initial biopsy specimen. Cessation of smoking may reverse or stabilize mild or moderate dysplasia. Some patients—estimated to be less than 5% of those with mild dysplasia and about 35–60% of those with severe dysplasia—will subsequently develop squamous cell carcinoma. Treatment options include PPI therapy, close follow-up with laryngovideostroboscopy, serial resection, and external beam radiation therapy.

Sezen Goktas S et al. A new approach to vocal cord leukoplakia and evaluation of proton pump inhibitor treatment. Eur Arch Otorhinolaryngol. 2019;276:467. [PMID: 30607560]

3. Squamous Cell Carcinoma of the Larynx

ESSENTIALS OF DIAGNOSIS

- New and persistent (> 2 weeks' duration) voice changes and hoarseness, especially in a smoker.
- Persistent throat pain, especially with swallowing; weight loss; neck mass; hemoptysis.
- Stridor or other symptoms of a compromised airway.

General Considerations

Squamous cell carcinoma of the larynx, the most common malignancy of the larynx, occurs almost exclusively in patients with a history of significant tobacco use. Based on a 2020 study, the incidence, prevalence, and mortality of laryngeal cancer are estimated at 2.76 cases/year per 100,000 individuals, 14.33 cases/year per 100,000 individuals and 1.66 deaths/year per 100,000 individuals, respectively. The incidence and prevalence have increased by 12% and 24%, respectively, during the past three decades. Mortality has declined by approximately 5%. Squamous cell carcinoma is usually seen in men aged 50–70 years. There may be an association between laryngeal cancer and HPV type 16 or 18 infection, but this association is much less strong than that between HPV 16 or 18 and oropharyngeal cancer. In both cancer types, the association with HPV seems to be strongest in nonsmokers. Laryngeal cancer is very treatable and early detection is the key to maximizing posttreatment voice, swallowing, and breathing function.

Clinical Findings

A. Symptoms and Signs

A change in voice quality is most often the presenting complaint, although throat or ear pain, hemoptysis, dysphagia, weight loss, and airway compromise may occur. Because of their early impact on vocal quality, glottic cancers are among the smallest detectable human malignancies and treatment success is very high with early lesions. Neck metastases are not common in early glottic (true vocal fold) cancer in which the vocal folds are mobile, but a third of patients in whom there is impaired fold mobility will also have involved lymph nodes at neck dissection. Supraglottic carcinoma (false vocal folds, aryepiglottic folds, epiglottis), on the other hand, often metastasizes to both sides of the neck early in the disease. Complete head and neck examination, including laryngoscopy, is mandatory for any person with the concerning symptoms listed under Essentials of Diagnosis.

B. Imaging and Laboratory Studies

Radiologic evaluation by CT or MRI is helpful in assessing tumor extent. Imaging evaluates neck nodes, tumor volume, and cartilage sclerosis or destruction. A chest CT scan is indicated if there are level VI enlarged nodes (around the trachea and the thyroid gland) or level IV enlarged nodes (inferior to the cricoid cartilage along the internal jugular vein), or if a chest film is concerning for a second primary lesion or metastases. Laboratory evaluation includes CBC and liver biochemical tests. Formal cardiopulmonary evaluation may be indicated, especially if partial laryngeal surgery is being considered. All partial laryngectomy candidates should have good to excellent lung function and exercise tolerance because chronic microaspiration may be expected following the procedure. A PET scan or CT-PET scan may be indicated to assess for distant metastases when there appears to be advanced local or regional disease.

C. Biopsy

Diagnosis is made by biopsy at the time of laryngoscopy when true fold mobility and arytenoid fixation, as well as surface tumor extent, can be evaluated. Most otolaryngologists recommend esophagoscopy and bronchoscopy at the same time to exclude synchronous primary tumor. Although an FNA biopsy of an enlarged neck node may have already been done, it is generally acceptable to assume radiographically enlarged neck nodes (greater than 1–1.5 cm) or nodes with necrotic centers are neck metastases. Open biopsies of nodal metastases should be discouraged because they may lead to higher rates of tumor treatment failure.

D. Tumor Staging

The American Joint Committee on Cancer (AJCC) staging of laryngeal cancers uses the TNM system to describe tumor extent and can be used for prognosis. Early laryngeal cancers, T1 and T2 (stage I and II) lesions, involve 1–2 laryngeal subsites locally and have no nodal metastases or profound functional abnormalities. T3 and T4 lesions may involve multiple laryngeal subsites with limitation of laryngeal mobility. These locally advanced lesions are stage III or IV cancers, and any size tumor with regional nodal metastases is at least a stage III tumor. Stage I and II lesions are generally treated with single-modality therapy (surgery or radiation), while multimodality therapy, usually including chemotherapy with radiation therapy, is reserved for more advanced stage III and IV lesions.

Treatment

Treatment of laryngeal carcinoma has four goals: cure, preservation of safe and effective swallowing, preservation of useful voice, and avoidance of a permanent tracheostoma. For early glottic and supraglottic cancers, radiation therapy is the standard of care since cure rates are greater than 95% and 80%, respectively. That said, radiation therapy carries substantial morbidity, and many early tumors (T1 and T2 lesions, without involved nodes) and selected advanced tumors (T3 and T4) may be treated with partial laryngectomy if at least one cricoarytenoid unit can be preserved. Five-year locoregional cure rates exceed 80–90% with surgery, and patient-reported satisfaction is excellent. In supraglottic tumors, even when clinically N0, elective limited neck dissection is indicated following surgical resection because of the high risk of neck node involvement.

Advanced stage III and IV tumors represent a challenging and ever-changing treatment dilemma. Twenty-five years ago, total laryngectomy was often recommended for such patients. However, the 1994 VA study (with induction cisplatin and 5-fluorouracil followed by irradiation alone in responders) demonstrated that two-thirds of patients could preserve their larynx. Subsequent studies have further defined multimodal therapy. Cisplatin-based chemotherapy concomitant with radiation therapy has been shown to be superior to either irradiation alone or induction chemotherapy followed by radiation. The same benefits have been demonstrated with the epidermal growth factor receptor blocker cetuximab with lower overall systemic toxicity and better patient tolerance. However, chemoradiation using either cetuximab or cisplatin is associated with prolonged gastrostomy-dependent dysphagia.

The high rate of dysphagia and morbidity associated with severe laryngeal stenosis following chemoradiation has prompted a reevaluation of the role of extended, but less-than-total, laryngeal resection for selected advanced laryngeal carcinoma in which at least one cricoarytenoid unit is intact (**organ preservation surgery**). In addition to the late complications, clinicians have noted that the overall success in the treatment of larynx cancer has declined in parallel with the increase in organ preservation chemoradiation therapy over the past 20 years. Some experts have proposed that this decline is the direct result of the shift in management of advanced laryngeal cancer away from surgery. Organ preservation surgery should be considered and discussed as an alternative to chemoradiation but may require referral to an appropriate regional center where such techniques are offered. After thorough evaluation of candidacy and discussion of the treatment options, patient choice plays a critical role in the ultimate decision to pursue surgery or chemoradiation as a definitive treatment modality. The patient and treating clinicians must carefully consider different early and late side effects and complications associated with different treatment modalities.

The presence of malignant adenopathy in the neck affects the prognosis greatly. Supraglottic tumors metastasize early and bilaterally to the neck, and this must be included in the treatment plans even when the neck is apparently uninvolved. Glottic tumors in which the true vocal folds are mobile (T1 or T2) have less than a 5% rate of nodal involvement; when a fold is immobile, the rate of ipsilateral nodal involvement climbs to about 30%. An involved neck is treated by surgery or chemoradiation, or both. This decision will depend on the treatment chosen for the larynx and the extent of neck involvement.

Total laryngectomy is largely reserved for patients with advanced resectable tumors with extralaryngeal spread or cartilage involvement, for those with persistent tumor following chemoradiation, and for patients with recurrent or second primary tumor following previous radiation therapy. Voice rehabilitation via a primary (or at times secondary) tracheoesophageal puncture produces intelligible and serviceable speech in about 75–85% of patients. Indwelling prostheses that are changed every 3–6 months are a common alternative to patient-inserted prostheses, which need changing more frequently.

Long-term follow-up is critical in head and neck cancer patients. In addition to the 3–4% annual rate of second tumors and monitoring for recurrence, psychosocial aspects of treatment are common. Dysphagia, impaired communication, and altered appearance may result in patient difficulties adapting to the workplace and to social interactions. In addition, smoking cessation and alcohol abatement are common challenges. Nevertheless, about 65% of patients with larynx cancer are cured, most have useful speech, and many resume their prior livelihoods with adaptations.

When to Refer

- Specialty referral should be sought early for diagnosis and treatment.
- Indirect or fiberoptic examination of the nasopharynx, oropharynx, hypopharynx, and larynx by an otolaryngologist–head and neck surgeon should be considered for patients with oral erythroplakia, unexplained throat or ear pain, unexplained oral or nasal bleeding, firm neck mass, or visible oral cavity or oropharyngeal mass.

When to Admit

- Airway compromise, hemorrhage, dehydration, significant weight loss.
- To determine an effective pain management regimen for severe pain.

Hrelec C. Management of laryngeal dysplasia and early invasive cancer. Curr Treat Options Oncol. 2021;22:90. [PMID: 34424405]

VOCAL FOLD PARALYSIS

Vocal fold paralysis can result from a lesion or damage to either the vagus or recurrent laryngeal nerve. It may result in breathy dysphonia, effortful voicing, aspiration, and rarely airway compromise. Common causes of **unilateral recurrent laryngeal nerve** involvement include thyroid surgery (and occasionally thyroid cancer), other neck surgery (anterior discectomy and carotid endarterectomy), and mediastinal or apical involvement by lung cancer. Skull base tumors often involve or abut upon lower cranial nerves and may affect the vagus nerve directly, or the vagus nerve may be damaged during surgical management of the lesion. While iatrogenic injury is the most common cause of unilateral vocal fold paralysis, the second most common cause is idiopathic. However, before deciding whether the paralysis is due to iatrogenic injury or is idiopathic, the clinician must exclude other causes, such as malignancy. In the absence of other cranial neuropathies, a CT scan with contrast from the skull base to the aorto-pulmonary window (the span of the recurrent laryngeal nerve) should be performed. If other cranial nerve deficits or high vagal weakness with palate paralysis is noted, an MRI scan of the brain and brainstem is warranted.

Unilateral vocal fold paralysis is occasionally temporary and may take over a year to resolve spontaneously. Surgical management of persistent or irrecoverable symptomatic unilateral vocal fold paralysis has evolved over the last several decades. The primary goal is medialization of the paralyzed fold in order to create a stable platform for vocal fold vibration. Additional goals include advancing diet and improving pulmonary toilet by facilitating cough. Success has been reported for years with injection laryngoplasty using Teflon, Gelfoam, fat, and collagen. Once the paralysis is determined to be permanent, formal medialization thyroplasty may be performed by creating a small window in the thyroid cartilage and placing an implant between the thyroarytenoid muscle and inner table of the thyroid cartilage. This procedure moves the vocal fold medially and creates a stable platform for bilateral, symmetric mucosal vibration.

Unlike unilateral fold paralysis, **bilateral fold paralysis** usually causes inspiratory stridor with deep inspiration and may cause rapid airway compromise. If the onset of bilateral fold paralysis is insidious, it may be asymptomatic at rest, and the patient may have a normal voice. However, the acute onset of bilateral vocal fold paralysis with inspiratory stridor at rest should be managed by a specialist immediately in a critical care environment. Causes of bilateral fold paralysis include thyroid surgery, esophageal cancer, and ventricular shunt malfunction. Unilateral or bilateral fold immobility may also be seen in trauma, cricoarytenoid arthritis secondary to advanced rheumatoid arthritis, intubation injuries, glottic and subglottic stenosis, and laryngeal cancer. The goal of intervention is the creation of a safe airway with minimal reduction in voice quality and airway protection from aspiration. A number of fold lateralization procedures for bilateral paralysis have been advocated as a means of removing the tracheotomy tube.

van Lith-Bijl JT et al. Laryngeal reinnervation: the history and where we stand now. Adv Otorhinolaryngol. 2020;85:98. [PMID: 33166981]

CRICOTHYROTOMY & TRACHEOSTOMY

The three main approaches to secure an airway include endotracheal intubation, cricothyrotomy, and tracheostomy. In an acute airway emergency where the airway above the trachea is blocked (ie, due to trauma, mass, or bleeding), cricothyrotomy secures an airway more rapidly than tracheotomy, with fewer potential immediate complications (eg, pneumothorax and hemorrhage). Depending on the airway emergency, a cricothyrotomy may need to be converted to a tracheostomy after the airway has been secured.

There are two primary indications for tracheotomy: airway obstruction at or above the level of the larynx and respiratory failure requiring prolonged mechanical ventilation. Tracheotomies may be performed via an open or percutaneous approach. In experienced hands, the various methods of percutaneous tracheotomy have been documented to be safe for carefully selected patients. Simultaneous videobronchoscopy can reduce the incidence of major complications. The major cost reduction comes from avoiding the operating room. Bedside tracheotomy (in the ICU) achieves similar cost reduction and is advocated by some experts as slightly less costly than the percutaneous procedures.

The most common indication for elective tracheotomy is the need for prolonged mechanical ventilation. There is no firm rule about how many days a patient must be intubated before conversion to tracheotomy should be advised. The incidence of serious complications, such as subglottic stenosis, increases with extended endotracheal intubation. **As soon as it is apparent that the patient will require protracted ventilatory support, tracheotomy should replace the endotracheal tube.** Less frequent indications for tracheostomy are life-threatening aspiration pneumonia,

the need to improve pulmonary toilet to correct problems related to insufficient clearing of tracheobronchial secretions, and obstructive sleep apnea.

Posttracheotomy care requires humidified air to prevent secretions from crusting and occluding the inner cannula of the tracheotomy tube. The tracheotomy tube should be cleaned several times daily. The most frequent early complication of tracheotomy is dislodgment of the tracheotomy tube. Surgical creation of an inferiorly based tracheal flap sutured to the inferior neck skin may make reinsertion of a dislodged tube easier. It should be recalled that the act of swallowing requires elevation of the larynx, which is limited by tracheotomy. Therefore, frequent tracheal and bronchial suctioning is often required to clear the aspirated saliva as well as the increased tracheobronchial secretions. Care of the skin around the tracheostoma is important to prevent maceration and secondary infection.

McGrath BA et al. Tracheostomy in the COVID-19 era: global and multidisciplinary guidance. Lancet Respir Med. 2020;8:717. [PMID: 32422180]
Pandian V et al. Critical care guidance for tracheostomy care during the COVID-19 pandemic: a global, multidisciplinary approach. Am J Crit Care. 2020;29:e116. [PMID: 32929453]

FOREIGN BODIES IN THE UPPER AERODIGESTIVE TRACT

FOREIGN BODIES IN THE TRACHEA & BRONCHI

Aspiration of foreign bodies occurs much less frequently in adults than in children. Older adults and denture wearers appear to be at greatest risk. Wider familiarity with the Heimlich maneuver has reduced deaths. If the maneuver is unsuccessful, cricothyrotomy may be necessary in the acute setting.

If there is no airway compromise, plain chest radiographs may reveal a radiopaque foreign body. Detection of radiolucent foreign bodies may be aided by CT or inspiration-expiration films that demonstrate air trapping distal to the obstructed segment. Atelectasis and pneumonia may occur later. Tracheal and bronchial foreign bodies should be removed under general anesthesia with rigid or flexible bronchoscopy by a skilled endoscopist working with an experienced anesthesiologist.

FOREIGN BODIES IN THE ESOPHAGUS

Foreign bodies in the esophagus create are typically not life-threatening situations. However, the acuity may rise depending on the type of foreign body (eg, a button battery) or if the airway is compromised. **Button battery ingestion is a surgical emergency.** If there is no concern for caustic ingestion or airway compromise, there is typically time to consult an otolaryngologist for management. It is a useful diagnostic sign of complete obstruction if the patient is drooling or cannot handle secretions. Patients may often point to the exact level of the obstruction. Indirect laryngoscopy often shows pooling of saliva at the esophageal inlet. Plain films may detect radiopaque foreign bodies, such as chicken bones. Coins tend to align in the coronal plane in the esophagus and in the sagittal direction in the trachea. If a foreign body is suspected, a CT or barium swallow may also help make the diagnosis.

The treatment of an esophageal foreign body depends on identification of its cause. In children, swallowed nonfood objects are common. In adults, however, food foreign bodies are more common, and there is the greater possibility of underlying esophageal pathology. If there is nothing sharp, such as a bone, some clinicians advocate a hospitalized 24-hour observation period prior to esophagoscopy, noting that spontaneous passage of the foreign body will occur in 50% of adult patients. In the management of meat obstruction, the use of papain (meat tenderizer) should be discouraged because it can damage the esophageal mucosa and lead to stenosis or perforation. Esophageal foreign bodies that do not pass need to be removed surgically. Endoscopic removal and examination are usually best via flexible esophagoscopy or rigid laryngoscopy and esophagoscopy. Complications of penetrating or erosive esophageal foreign bodies may include mediastinitis or erosion in the trachea with associated tracheitis.

Chirica M et al. Esophageal emergencies: WSES guidelines. World J Emerg Surg. 2019;14:26. [PMID: 31164915]

DISEASES PRESENTING AS NECK MASSES

The differential diagnosis of neck masses is heavily dependent on the location in the neck, the age of the patient, and the presence of associated disease processes. Rapid growth and tenderness suggest an inflammatory process, while firm, painless, and slowly enlarging masses are often neoplastic. In young adults, most neck masses are benign (branchial cleft cyst, thyroglossal duct cyst, reactive lymphadenitis), although malignancy should always be considered (lymphoma, metastatic thyroid carcinoma). Lymphadenopathy is common in HIV-positive persons, but a growing or dominant mass may well represent lymphoma. **In adults over age 40, cancer is the most common cause of persistent neck mass and should be definitively ruled out.** A metastasis from squamous cell carcinoma arising within the mouth, pharynx, larynx, or upper esophagus should be suspected. Risk factors for squamous cell carcinoma include smoking and HPV exposure. Especially among patients younger than 30 or older than 70, lymphoma also should be considered. In all cases, a comprehensive otolaryngologic examination is needed. Imaging and pathologic evaluation of the neck mass via FNA biopsy is likely to be the next step if a primary tumor is not obvious on physical examination.

CONGENITAL LESIONS PRESENTING AS NECK MASSES IN ADULTS

1. Branchial Cleft Cysts

Branchial cleft cysts usually present as a soft cystic mass along the anterior border of the sternocleidomastoid muscle. These lesions are usually recognized in the second or

third decades of life, often when they suddenly swell or become infected. To prevent recurrent infection and possible carcinoma, they should be completely excised, along with their fistulous tracts.

First branchial cleft cysts present high in the neck, sometimes just below the ear. A fistulous connection with the floor of the external auditory canal may be present. Second branchial cleft cysts, which are far more common, may communicate with the tonsillar fossa. Third branchial cleft cysts, which may communicate with the piriform sinus, are rare and present low in the neck.

2. Thyroglossal Duct Cysts

Thyroglossal duct cysts occur along the embryologic course of the thyroid's descent from the tuberculum impar of the tongue base to its usual position in the low neck. Although they may occur at any age, they are most common before age 20. They present as a midline neck mass, often just below the hyoid bone, which moves with swallowing. Surgical excision is recommended to prevent recurrent infection and rare malignancy. This requires removal of the entire fistulous tract along with the middle portion of the hyoid bone through which many of the fistulas pass. CT or ultrasound or both are often obtained preoperatively to understand associated neck anatomy, including position of the thyroid.

INFECTIOUS & INFLAMMATORY NECK MASSES

1. Reactive Cervical Lymphadenopathy

Normal lymph nodes in the neck are usually less than 1 cm in length. Infections involving the pharynx, salivary glands, and scalp often cause tender enlargement of neck nodes. Enlarged nodes are common in HIV-infected persons. Except for the occasional node that suppurates and requires incision and drainage, treatment is directed against the underlying infection. An enlarged node (larger than 1.5 cm) or node with a necrotic center that is not associated with an obvious infection should be further evaluated, especially if the patient has a history of smoking, alcohol use, or prior cancer. Other common indications for FNA biopsy of a node include its persistence or continued enlargement. Common causes of cervical adenopathy include cancer (eg, squamous cell carcinoma, lymphoma, occasional metastases from non-head and neck sites) and infection (eg, reactive nodes, mycobacteria, and cat-scratch disease). Rare causes of adenopathy include Kikuchi disease (histiocytic necrotizing lymphadenitis) and autoimmune adenopathy.

2. Tuberculous & Nontuberculous Mycobacterial Lymphadenitis

Granulomatous neck masses are uncommon in the United States unless there are specific risk factors for particular infectious exposures or granulomatous hereditary or autoimmune illness. The differential diagnosis includes mycobacterial adenitis, sarcoidosis, and cat-scratch disease due to *Bartonella henselae*. The incidence of mycobacterial lymphadenitis is on the rise both in immunocompromised and immunocompetent individuals. The usual presentation of granulomatous disease in the neck is simply single or matted nodes. Although mycobacterial adenitis can extend to the skin and drain externally (as described for atypical mycobacteria and referred to as scrofula), this late presentation is no longer common.

FNA biopsy is usually the best initial diagnostic approach: cytology, smear for acid-fast bacilli, mycobacterial culture, and a sensitivity test can all be done. PCR from FNA (or from excised tissue) is the most sensitive test and is particularly useful when conventional methods have not been diagnostic but clinical impression remains consistent for tuberculous infection. While FNA has a high sensitivity (about 88%), its specificity is low (49%); thus, an excisional biopsy is often required to confirm the diagnosis.

See Tables 9–14 and 9–15 for current recommended treatment of tuberculosis infection, which includes infection of the lymph nodes (tuberculous lymphadenopathy). For atypical (nontuberculous) infection of the lymph nodes, treatment depends on the sensitivity results of culture, but antibiotics likely to be useful include 6 months of isoniazid and rifampin and, for at least the first 2 months, ethambutol—all in standard dosages. Some would totally excise the involved nodes prior to chemotherapy, depending on location and other factors, but this can lead to chronic draining fistulas.

3. Lyme Disease

Lyme disease, caused by the spirochete *Borrelia burgdorferi* and transmitted by ticks of the *Ixodes* genus, may have protean manifestations, but over 75% of patients have symptoms involving the head and neck. Facial paralysis, hearing loss, dysesthesias, dysgeusia, or other cranial neuropathies are most common. Headache, pain, and cervical lymphadenopathy may occur. It is essential to ask patients with cranial neuropathies about risk factors for Lyme disease. See Chapter 34 for a more detailed discussion.

Zhou G et al. Antibiotic prophylaxis for prevention against Lyme disease following tick bite: an updated systematic review and meta-analysis. BMC Infect Dis. 2021;21:1141. [PMID: 34749665]

CANCER METASTASES

In older adults, 80% of firm, persistent, and enlarging neck masses are metastatic in origin. The majority of these arise from squamous cell carcinoma of the upper aerodigestive tract, such as nasopharynx, tonsils, tongue base, and larynx. A complete head and neck examination may reveal the cancer of origin, but often imaging and examination under anesthesia are necessary to detect the primary lesion. Detecting the primary lesion is essential since it may directly impact oncologic treatment modalities. Initial radiologic screening exams typically include a CT, MRI, or PET. After imaging, many patients require direct laryngoscopy, esophagoscopy, and tracheobronchoscopy to further elucidate the primary lesion. At this time, biopsies may be taken for suspicious lesions. Fine-needle aspiration of neck

masses are also routine and may help determine the diagnosis while evaluation of the primary malignancy is ongoing. Open neck biopsy should only be performed by head and neck surgeons experienced in the management of head and neck cancer since complications from open biopsy may make subsequent formal neck dissections more challenging if cancer is detected. With the exception of papillary thyroid carcinoma, non–squamous cell metastases to the neck are infrequent. While cancers that are not primary in the head or neck seldom metastasize to the cervical lymph nodes, the supraclavicular lymph nodes are quite often involved by lung, gastroesophageal, and breast cancers. Infradiaphragmatic cancers, with the exception of renal cell carcinoma and testicular cancer, rarely metastasize to the neck.

Pellini R et al. Narrow band imaging in head and neck unknown primary carcinoma: a systematic review and meta-analysis. Laryngoscope. 2020;130:1692. [PMID: 31714611]

LYMPHOMA

About 10% of lymphomas present in the head and neck. Multiple rubbery nodes, especially in young adults or in patients who have AIDS, are suggestive of lymphoma. A thorough physical examination may demonstrate other sites of nodal or organ involvement. FNA biopsy may be diagnostic, but open biopsy is often required to determine architecture and an appropriate treatment course.

Cabeçadas J et al. Lymphomas of the head and neck region: an update. Virchows Arch. 2019;474:649. [PMID: 30778677]
Payabvash S et al. Differentiation of lymphomatous, metastatic, and non-malignant lymphadenopathy in the neck with quantitative diffusion-weighted imaging: systematic review and meta-analysis. Neuroradiology. 2019;61:897. [PMID: 31175398]

9 Pulmonary Disorders

Meghan E. Fitzpatrick, MD
Niall T. Prendergast, MD
Belinda Rivera-Lebron, MD, MS, FCCP

DISORDERS OF THE AIRWAYS

Disorders of the airways can be classified as those that involve the upper airways—loosely defined as those above and including the vocal folds—and those that involve the lower airways.

DISORDERS OF THE UPPER AIRWAYS

Acute obstruction of the upper airway can be immediately life-threatening and must be relieved promptly to avoid asphyxia. Causes of acute upper airway obstruction include trauma to the larynx or pharynx, foreign body aspiration, laryngospasm, laryngeal edema from thermal injury or angioedema, infections (acute epiglottitis, Ludwig angina, pharyngeal or retropharyngeal abscess), and acute allergic laryngitis.

Chronic obstruction of the upper airway may be caused by goiter, carcinoma of the pharynx or larynx, laryngeal or subglottic stenosis, laryngeal granulomas or webs, or bilateral vocal fold paralysis. Laryngeal or subglottic stenosis may become evident weeks or months after endotracheal intubation. Laryngomalacia refers to the collapse of the supraglottic structures during inspiration. It is the most common congenital anomaly of the larynx, manifests in infancy, and is usually resolved by 12–18 months. Inspiratory stridor, intercostal retractions on inspiration, a palpable inspiratory thrill over the larynx, and wheezing localized to the neck or trachea on auscultation are characteristic findings. Flow-volume loops may show characteristic flow limitations. Soft-tissue radiographs of the neck may show supraglottic or infraglottic narrowing. CT and MRI scans can reveal exact sites of obstruction. Flexible endoscopy may be diagnostic, but caution is necessary to avoid exacerbating upper airway edema and precipitating critical airway narrowing.

Vocal fold dysfunction syndrome, a type of inducible laryngeal obstruction, is characterized by paradoxical vocal fold adduction causing acute or chronic upper airway obstruction, or both. It presents as dyspnea and wheezing that may mimic asthma but may be distinguished from asthma or exercise-induced asthma by the lack of response to bronchodilator therapy, normal spirometry immediately after an attack, spirometric evidence of upper airway obstruction in a flow-volume loop, and a negative bronchial provocation test. However, vocal fold dysfunction may coexist with asthma, be induced by exercise, inhalational irritant exposures, laryngopharyngeal reflux of gastric contents, or psychological stress. Definitive diagnosis requires direct visualization of adduction of the vocal folds on inspiration. Treatment consists of addressing underlying precipitants (including psychogenic contributors), and speech therapy.

Eskander A et al. Acute upper airway obstruction. N Engl J Med. 2019;381:1940. [PMID: 31722154]
Petrov AA. Vocal cord dysfunction: the spectrum across the ages. Immunol Allergy Clin North Am. 2019;39:547. [PMID: 31563188]

DISORDERS OF THE LOWER AIRWAYS

Tracheal obstruction may be intrathoracic (below the suprasternal notch) or extrathoracic. Fixed tracheal obstruction may be caused by acquired or congenital tracheal stenosis, primary or secondary tracheal neoplasms, extrinsic compression (tumors of the lung, thymus, or thyroid; lymphadenopathy; congenital vascular rings; aneurysms; etc), foreign body aspiration, tracheal granulomas and papillomas, tracheal trauma, or idiopathic subglottic stenosis. Variable or dynamic tracheal obstruction may be caused by tracheomalacia, foreign body aspiration, and retained secretions.

Acquired **tracheal stenosis** is usually secondary to previous tracheotomy or endotracheal intubation. Dyspnea, cough, and inability to clear pulmonary secretions occur weeks to months after tracheal decannulation or extubation. Physical findings may be absent until tracheal diameter is reduced 50% or more, when wheezing, a palpable tracheal thrill, and harsh breath sounds may be detected. The diagnosis is usually confirmed by plain films or CT of the trachea. Complications include recurring pulmonary infection and life-threatening respiratory failure. Management is directed toward ensuring adequate ventilation and oxygenation and avoiding manipulative procedures that may increase edema of the tracheal mucosa. Surgical

reconstruction, endotracheal stent placement, or laser photoresection may be required.

Bronchial obstruction may be caused by retained pulmonary secretions, aspiration, foreign bodies, bronchomalacia, bronchogenic carcinoma, compression by extrinsic masses, and tumors metastatic to the airway. Clinical and radiographic findings vary depending on the location of the obstruction and the degree of airway narrowing. Symptoms include dyspnea, cough, wheezing, and, if infection is present, fever and chills. A history of recurrent pneumonia in the same lobe or segment or slow resolution (more than 3 months) of pneumonia on successive radiographs suggests the possibility of bronchial obstruction and the need for bronchoscopy.

Radiographic findings include atelectasis (local parenchymal collapse), postobstructive infiltrates, and air trapping caused by unidirectional expiratory obstruction. CT scanning may demonstrate the nature and exact location of obstruction. Bronchoscopy is the definitive diagnostic study, particularly if tumor or foreign body aspiration is suspected. Management includes the use of bronchoscopic electrocautery, argon plasma coagulation, and laser and radiofrequency ablation.

Halvorsen T et al. Conundrums of exercise-related breathing problems. Epiglottic, laryngeal, or bronchial obstruction? Am J Respir Crit Care Med. 2020;202:e142. [PMID: 32783778]

Mahajan AK et al. Electrosurgical and laser therapy tools for the treatment of malignant central airway obstructions. Chest. 2020;157:446. [PMID: 31472155]

ASTHMA

ESSENTIALS OF DIAGNOSIS

- Episodic or chronic symptoms of wheezing, dyspnea, or cough.
- Symptoms frequently worse at night or in the early morning.
- Prolonged expiration and diffuse wheezes on physical examination.
- Limitation of airflow on pulmonary function testing (PFT) or positive bronchoprovocation challenge.
- Reversibility of airflow obstruction, either spontaneously or following bronchodilator therapy.

General Considerations

Asthma is a common disease, affecting approximately 8–10% of the population. It is slightly more common in male children (younger than 14 years) and in female adults. There is a genetic predisposition to asthma. Prevalence, hospitalizations, and fatal asthma have all increased in the United States over the past 20 years. Each year, approximately 10 million office visits, 1.8 million emergency department visits, and more than 3500 deaths in the United States are attributed to asthma. Hospitalization rates are highest among Black persons and children, and death rates are consistently highest among Black persons aged 15–24 years. The 2020 Global Initiative for Asthma (GINA) Report entitled *Global Strategy for Asthma Management and Prevention* is a comprehensive and practical resource that addresses asthma diagnosis, assessment, management, and exacerbations.

Definition & Pathogenesis

Asthma is a chronic disorder of the airways characterized by variable airway obstruction, airway hyperresponsiveness, and airway inflammation. No single histopathologic feature is pathognomonic but common findings include airway inflammatory cell infiltration with eosinophils, neutrophils, and lymphocytes (especially T cells); goblet cell hyperplasia; plugging of small airways with mucus; collagen deposition beneath the basement membrane; bronchial smooth muscle hypertrophy; airway edema; mast cell activation; and denudation of airway epithelium. The pathophysiology of asthma is heterogeneous, but a division into T2-high and T2-low endotypes (marked by high and low levels, respectively, of classic Th2 cytokines such as interleukin [IL]-4, IL-5, and IL-13) has been shown to be important regarding the selection of therapies.

Many clinical phenotypes of asthma have been identified. The most common is **allergic asthma,** which usually begins in childhood and is associated with other allergic diseases such as eczema, allergic rhinitis, or food allergy. Exposure of sensitive patients to inhaled allergens may cause symptoms immediately (immediate asthmatic response) or 4–6 hours after allergen exposure (late asthmatic response). Common allergens include house dust mites (often found in pillows, mattresses, upholstered furniture, carpets, and drapes), cockroaches, cat dander, and seasonal pollens. **Allergic asthma** falls into the T2-high endotype, as do **late-onset** T2-high asthma and **aspirin/NSAID-associated respiratory disease.** T2-low asthma phenotypes include **nonallergic asthma**, which tends to occur in adults and be marked by neutrophilic inflammation and variable response to standard therapies. **Asthma with persistent airflow limitation** is thought to be due to airway remodeling. **Asthma with obesity** refers to prominent respiratory symptoms in obese patients with little airway inflammation.

Nonspecific precipitants of asthma include upper respiratory tract infections, rhinosinusitis, postnasal drip, aspiration, gastroesophageal reflux, changes in the weather, stress, and exercise. Exposure to **products of combustion** (eg, from tobacco, methamphetamines, diesel fuel, and other agents) increases asthma symptoms and the need for medications and reduces lung function. **Air pollution** (increased air levels of respirable particles, ozone, SO_2, and NO_2) precipitates asthma symptoms and increases emergency department visits and hospitalizations. Selected individuals may experience asthma symptoms after exposure to aspirin (aspirin-exacerbated respiratory disease), NSAIDs, or tartrazine dyes. Other **medications** may

precipitate asthma symptoms (see Table 9–23). **Occupational asthma** is triggered by various agents in the workplace and may occur weeks to years after initial exposure and sensitization. Women may experience **catamenial asthma** at predictable times during the menstrual cycle. **Exercise-induced bronchoconstriction** begins during exercise or within 3 minutes after its end, peaks within 10–15 minutes, and then resolves by 60 minutes. This phenomenon is thought to be a consequence of the airways' warming and humidifying an increased volume of expired air during exercise. **Cough-variant asthma** has cough instead of wheezing as the predominant symptom of bronchial hyperreactivity. Other diseases may mimic asthma; **"cardiac asthma"** is wheezing precipitated by pulmonary edema in the setting of decompensated heart failure, while **upper airway obstruction** and **paradoxical vocal fold motion** may also present with wheezing and dyspnea.

Clinical Findings

Symptoms and signs vary widely among patients as well as within individuals over time. General clinical findings in stable asthma patients and findings seen during asthma exacerbations are listed in Table 9–1.

A. Symptoms and Signs

Asthma is characterized by episodic wheezing, shortness of breath, chest tightness, and cough. Symptoms vary over time and in intensity and are often worse at night or in the early morning. Asthma symptoms may occur spontaneously or be precipitated or exacerbated by many different triggers, as discussed above. The following features decrease the likelihood that respiratory symptoms are due to asthma: isolated cough with no other symptoms, chronic sputum production, chest pain, and shortness of breath with paresthesias.

Some physical examination findings increase the probability of asthma. Nasal mucosal swelling, increased secretions, and polyps are often seen in patients with allergic asthma. Eczema, atopic dermatitis, or other allergic skin disorders may also be present. Wheezing or a prolonged expiratory phase during normal breathing correlates well with the presence of airflow obstruction; wheezing during forced expiration does not. Chest examination may be normal between exacerbations in patients with mild asthma. During severe asthma exacerbations, airflow may be too limited to produce wheezing, and the only diagnostic clue on auscultation may be globally reduced breath sounds with prolonged expiration. Hunched shoulders and use of accessory muscles of respiration suggest an increased work of breathing.

B. Laboratory Findings

Arterial blood gas (ABG) measurements may be normal during a mild asthma exacerbation, but respiratory alkalosis and an increase in the alveolar-arterial oxygen difference ($A–a–Do_2$) are common. During severe exacerbations, hypoxemia develops and the $Paco_2$ returns to normal. The combination of an increased $Paco_2$ and respiratory acidosis may indicate impending respiratory failure and the need for mechanical ventilation.

C. Pulmonary Function Testing

Clinicians correctly identify airflow obstruction on examination but have limited ability to gauge its severity or to predict whether it is reversible. The evaluation for asthma should therefore include **spirometry** (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], and FEV_1/FVC) before and after the administration of a short-acting bronchodilator. These measurements help determine the presence and extent of airflow obstruction and whether it is immediately reversible. Airflow obstruction is indicated by a reduced FEV_1/FVC ratio, generally below 0.7. Significant reversibility of airflow obstruction is defined by an increase of 12% or more and 200 mL in FEV_1 or FVC after inhaling a short-acting bronchodilator. A positive bronchodilator response supports the diagnosis of asthma, but a lack of responsiveness in the pulmonary function laboratory does not preclude success in a clinical trial of bronchodilator therapy. Severe airflow obstruction results in significant air trapping, with an increase in residual volume and consequent reduction in FVC, resulting in a pattern that may mimic a restrictive ventilatory defect.

Table 9–1. Assessing asthma control.

Components of Asthma Control	Classification of Asthma Control		
	Well Controlled	Partly Controlled	Not Controlled
Daytime asthma symptoms > 2 ×/week Nighttime awakenings due to asthma Interference with normal activity due to asthma Reliever medication needed for asthma symptoms > 2 ×/week	None of these components within past 4 weeks	1 or 2 of these components within past 4 weeks	3 or 4 of these components within past 4 weeks

Adapted from National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Pub. No. 08-4051. Bethesda, MD, 2007, and Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. (Available from: www.ginasthma.org.)

Bronchoprovocation testing with inhaled histamine or methacholine may be useful when asthma is suspected but spirometry is nondiagnostic. Bronchial provocation is not recommended if the FEV_1 is less than 65% of predicted. A positive methacholine test is defined as a fall in the FEV_1 of 20% or more at exposure to a methacholine concentration of less than or equal to 8 mg/mL. A negative methacholine test has a negative predictive value for asthma of 95%. Exercise challenge testing may be useful in patients with symptoms of exercise-induced bronchospasm.

Peak expiratory flow (PEF) meters are handheld devices designed as personal monitoring tools. PEF monitoring can establish peak flow variability, quantify asthma severity, and provide both patient and clinician with objective measurements on which to base treatment decisions. There are conflicting data about whether measuring PEF improves asthma outcomes but doing so is recommended to help confirm the diagnosis of asthma, to improve asthma control in patients with poor perception of airflow obstruction, and to identify environmental and occupational causes of symptoms. Predicted values for PEF vary with age, height, and sex but are poorly standardized. Comparison with reference values is less helpful than comparison with the patient's own baseline. PEF shows diurnal variation; it is generally lowest on first awakening and highest several hours before the midpoint of the waking day. PEF should be measured in the morning before the administration of a bronchodilator and in the afternoon after taking a bronchodilator. A 20% change in PEF values from morning to afternoon or from day to day suggests inadequately controlled asthma. PEF values less than 200 L/minute indicate severe airflow obstruction.

D. Additional Testing

Routine chest radiographs in patients with asthma are usually normal or show only hyperinflation. Other findings may include bronchial wall thickening and diminished peripheral lung vascular markings. Chest imaging is indicated when pneumonia, another disorder mimicking asthma, or a complication of asthma such as pneumothorax is suspected.

Skin or in vitro testing, including total serum IgE and allergen-specific IgE, to assess sensitivity to environmental allergens can identify atopy in patients with persistent asthma who may benefit from therapies directed at their allergic diathesis. Evaluations for paranasal sinus disease or gastroesophageal reflux should be considered in patients with persistent, severe, or refractory asthma symptoms. An absolute eosinophil count can identify patients eligible for anti–IL-5 therapy to manage eosinophilic airway disease.

Complications

Complications of asthma include exhaustion, dehydration, airway infection, and tussive syncope. Pneumothorax occurs but is rare. Acute hypercapnic and hypoxemic respiratory failure occurs in severe disease.

Differential Diagnosis

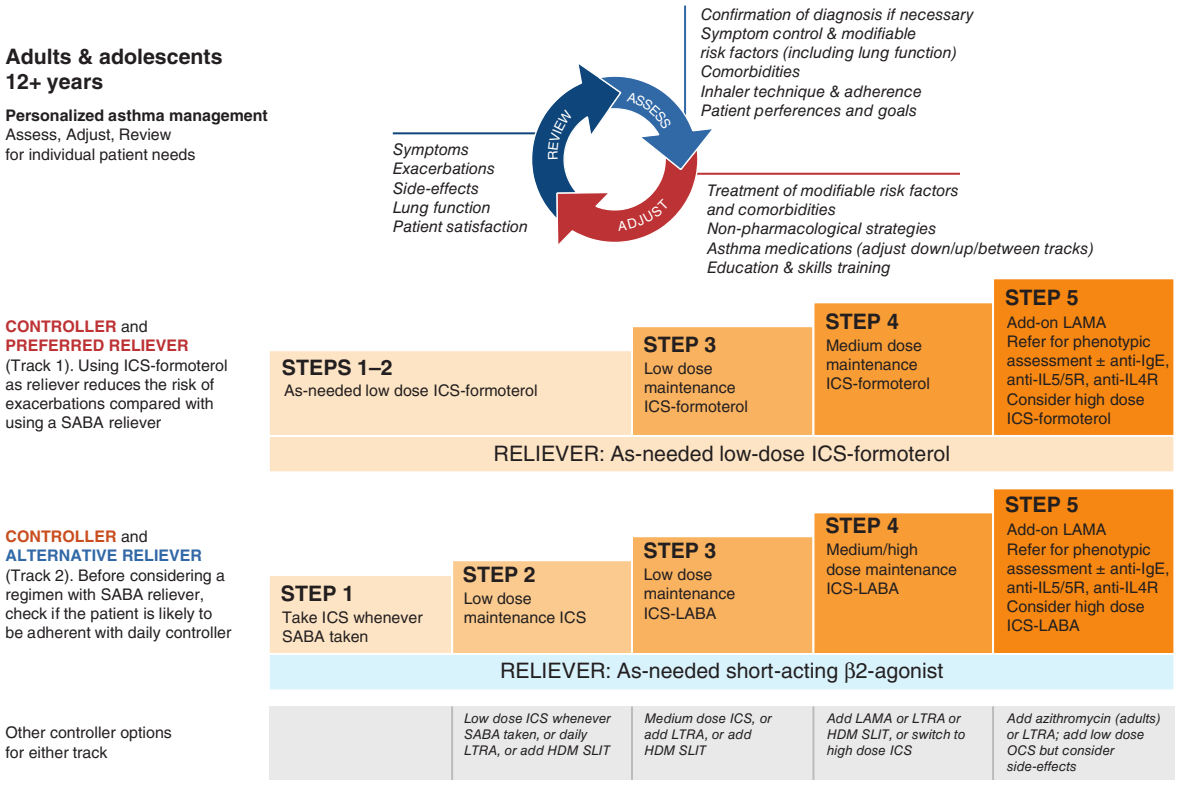
Patients who have atypical symptoms or poor response to therapy may have one of several conditions that mimic asthma. These disorders typically fall into upper airway disorders, lower airway disorders, systemic vasculitides, cardiac disorders, and psychiatric disorders. **Upper airway disorders** that mimic asthma include vocal fold paralysis, vocal fold dysfunction syndrome, narrowing of the supraglottic airway, and laryngeal masses or dysfunction. **Lower airway disorders** include foreign body aspiration, tracheal masses or narrowing, tracheobronchomalacia, airway edema (eg, angioedema or inhalation injury), nonasthmatic COPD (chronic bronchitis or emphysema), bronchiectasis, allergic bronchopulmonary aspergillosis (mycosis), cystic fibrosis, eosinophilic pneumonia, hypersensitivity pneumonitis, sarcoidosis, and bronchiolitis obliterans. A **systemic vasculitis** with pulmonary involvement may have an asthmatic component, such as eosinophilic granulomatosis with polyangiitis. **Cardiac disorders** include heart failure and pulmonary hypertension. **Psychiatric causes** include conversion disorders ("functional" asthma), emotional laryngeal wheezing, or episodic laryngeal dyskinesis. Rarely, Münchausen syndrome or malingering may explain a patient's complaints.

Approach to Management

The 2020 GINA Report *Global Strategy for Asthma Management and Prevention* provides guidelines for the management of asthma and identifies five important aspects of chronic asthma management: (1) assessing asthma control and severity, (2) distinguishing between severe asthma and uncontrolled asthma, (3) personalized pharmacologic therapy for asthma, (4) treatment of modifiable risk factors and control of environmental factors, and (5) guided self-management education and skills training.

1. Assessing asthma control and severity—Asthma control is assessed by evaluating symptoms, activity limitations, and risk of future exacerbations. Asthma symptoms are assessed by asking patients about their past 4 weeks including frequency of symptoms (days per week), awakening from sleep, and frequency of short-acting beta-agonist (SABA) use for relief of symptoms (Table 9–1). Future risk of exacerbations is increased by poor symptom control as well as several other risk factors: more than one exacerbation in the previous year, poor asthma medication adherence, incorrect inhaler technique, chronic sinusitis, and smoking. **Asthma severity** is evaluated retrospectively from the level of treatment needed to control symptoms and exacerbations. For example, a patient who requires Step 3 treatment to achieve control has moderate disease. Figure 9–1 describes the step therapy in a personalized asthma management plan. Typically, mild asthma responds to Step 1 or 2 treatments, moderate asthma to Step 3 treatment, and severe asthma to Step 4 or 5 treatments.

2. Uncontrolled vs severe asthma—It is important to distinguish between uncontrolled and severe asthma in patients who are using Step 4 or Step 5 treatments. The clinician must assess inhaler technique, medication adherence, comorbidities such as obstructive sleep apnea or GERD, and ongoing exposure to allergens as causes of poor



HDM: house dust mite; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist; SLIT: sublingual immunotherapy.

▲ **Figure 9–1.** Personalized management for adults and adolescents to control symptoms and minimize future risk. (Reproduced with permission from Global Strategy for Asthma Management and Prevention (updated 2019). Global Initiative for Asthma-GINA, 2019.)

asthma control ("uncontrolled" asthma). If the patient still requires Step 4 or 5 therapy after these issues have been addressed, then the patient has "severe" asthma and should be referred to a pulmonary or asthma specialist.

3. Pharmacotherapy for asthma—The goals of pharmacologic therapy are to minimize chronic symptoms that interfere with normal activity (including exercise), to prevent recurrent exacerbations, to reduce or eliminate the need for emergency department visits or hospitalizations, and to maintain normal or near-normal pulmonary function. Personalized asthma management is a continuous cycle that involves assessment, treatment, and review with the goals of symptom control and minimizing future risk. These goals should be met while providing therapeutic agents with the fewest adverse effects and while satisfying patients' expectations of asthma care. Management should include stepping up therapy if asthma remains uncontrolled despite adherence and good inhaler technique and stepping down to find the minimum effective therapeutic dose.

4. Treat modifiable risk factors and control environmental factors—Significant reduction in exposure to nonspecific airway irritants in all patients or to inhaled allergens in atopic patients may reduce symptoms and medication needs. Comorbid conditions that impair asthma management, such as smoking, rhinosinusitis, GERD, obesity, and obstructive sleep apnea, should be identified and treated. Nonpharmacologic interventions include increasing physical activity and breathing exercises.

5. Guided asthma self-management education and skills training—Self-management includes self-monitoring of symptoms or peak flow, a written action plan, and regular review of asthma control, treatment, and skills with a health care professional.

Treatment

A. Pharmacologic Agents

Asthma medications can be divided into three categories: (1) **long-term controller** medications (Table 9–2) used long-term to reduce airway inflammation, symptoms, and risk of future exacerbations, (2) **reliever** medications (Table 9–3) used on an as-needed basis to relieve breakthrough symptoms, and (3) **add-on therapies** for severe asthma. Figure 9–1 shows a personalized management plan for asthma to control symptoms and minimize future risk.

Most asthma medications are administered by inhalation or by oral dosing. Inhalation of an appropriate agent results in a more rapid onset of pulmonary effects as well as fewer systemic effects compared with the oral dose required to achieve the same effect on the airways. Proper inhaler technique and the use of an inhalation chamber (a "spacer") with metered-dose inhalers (MDIs) decrease oropharyngeal drug deposition and improve drug delivery to the lung. Nebulizer therapy is reserved for patients who are acutely ill and those who cannot use inhalers because of difficulties with coordination, understanding, or cooperation.

1. Inhaled corticosteroids—Inhaled corticosteroids are essential controller medications (Tables 9–3 and 9–4). Once the diagnosis of asthma is made, early initiation of inhaled corticosteroid therapy leads to a greater improvement in lung function than delayed therapy. Prescribing as-needed or daily controller inhaled corticosteroids at the start of asthma therapy conveys a message to patients that both symptom control and risk reduction are the mainstays of asthma treatment. The most important determinants of medication choice, device and dose are a patient's symptoms and risk factors, along with practical issues (such as cost and delivery mechanism). Inhaled corticosteroid dosages are classified as low-, medium-, and high-dose strengths in various published sources including GINA, but low-dose inhaled corticosteroid provides clinical benefit and is sufficient for most patients with asthma. Dosages for inhaled corticosteroids vary depending on the specific agent and delivery device (Table 9–4). For patients who require high-dose inhaled corticosteroids to achieve adequate symptom control, after 3 months of good control, the dose of inhaled corticosteroid should be decreased to the lowest dose that preserves symptom control and minimizes exacerbation risk.

Concomitant use of an MDI and an inhalation chamber coupled with mouth washing after inhaled corticosteroid use decreases systemic absorption and local side effects (cough, dysphonia, oropharyngeal candidiasis). Dry powder inhalers (DPIs) are not used with an inhalation chamber. Systemic effects (adrenal suppression, osteoporosis, skin thinning, easy bruising, and cataracts) may occur with high-dose inhaled corticosteroid therapy. Combination inhalers with an inhaled corticosteroid and a long-acting beta-2-agonist (LABA) offer convenient treatment of asthma. The GINA report recommends low-dose inhaled corticosteroid/formoterol as its preferred agent due to clinical evidence but notes that its cost and availability in different countries must be taken into consideration. Budesonide/formoterol is listed as a World Health Organization (WHO) essential medication.

2. Beta-adrenergic agonists—Beta-agonists are divided into SABAs and LABAs. SABAs (Table 9–3), including agents such as albuterol, levalbuterol, bitolterol, pirbuterol, and terbutaline, are mainstays of reliever or rescue therapy for asthma patients. There is no convincing evidence to support the use of one agent over another. All asthmatics should have immediate access to a SABA because they are the most effective bronchodilators during exacerbations and provide immediate relief of symptoms. Administration before exercise effectively prevents exercise-induced bronchoconstriction.

Inhaled SABA therapy is as effective as oral or parenteral beta-agonist therapy in relaxing airway smooth muscle and improving acute asthma and offers the advantages of rapid onset of action (less than 5 minutes) with fewer systemic side effects. Repetitive administration produces incremental bronchodilation. One or two inhalations of a

Table 9–2. Long-term controller medications for asthma.

Medication	Dosage Form	Adult Dose	Comments
Inhaled Corticosteroids (ICS)			**(See Table 9–4)**
Systemic Corticosteroids			**(Applies to all three corticosteroids)**
Methylprednisolone	2-, 4-, 6-, 8-, 16-, 32-mg tablets	40–60 mg	• Administer single dose in AM either daily or on alternate days (alternate-day therapy may produce less adrenal suppression) as needed for control. • Short courses or "bursts" as single or two divided doses for 3–10 days are effective for establishing control when initiating therapy or during a period of gradual deterioration. • There is no evidence that tapering the dose following improvement in symptom control and pulmonary function prevents relapse.
Prednisolone	5-mg tablets; 5 mg/5 mL, 15 mg/5 mL oral solution	40–60 mg	
Prednisone	1-, 2.5-, 5-, 10-, 20-, 50-mg tablets; 5 mg/mL oral solution	7.5–60 mg	
Inhaled LABA			**Should not be used for symptom relief or exacerbations. Use with inhaled corticosteroids.**
Formoterol	Inhalation: 20 mcg/2 mL nebulizer (DPI discontinued by FDA in United States)	20 mcg every 12 hours	• Additional doses should not be administered for at least 12 hours. • Agents should be used only with their specific inhaler and should not be taken orally. • Decreased duration of protection against EIB may occur with regular use.
Salmeterol	DPI: 50 mcg/actuation	1 blister every 12 hours	
Combined Medication			
Budesonide/formoterol	HFA MDI: 80 mcg/4.5 mcg 160 mcg/4.5 mcg	2 inhalations twice daily; dose depends on severity of asthma	• 80/4.5 mcg for asthma not controlled on low- to medium-dose ICS. • 160/4.5 mcg for asthma not controlled on medium- to high-dose ICS.
Fluticasone/salmeterol	DPI: 100 mcg/50 mcg 250 mcg/50 mcg 500 mcg/50 mcg HFA: 45 mcg/21 mcg 115 mcg/21 mcg 230 mcg/21 mcg	1 inhalation twice daily; dose depends on severity of asthma	• 100/50 mcg DPI or 45/21 mcg HFA for asthma not controlled on low- to medium-dose ICS. • 250/50 mcg DPI or 115/21 mcg HFA for asthma not controlled on medium- to high-dose ICS.
Fluticasone furoate/vilanterol	DPI: 100 mcg/25 mcg or 200 mcg/25 mcg per blister	1 puff inhaled daily	• Once-daily asthma maintenance.
Mometasone/formoterol	100 mcg/5 mcg/spray 200 mcg/5 mcg/spray	2 inhalations twice daily	
Cromolyn and Nedocromil			
Cromolyn	MDI: 0.8 mg/puff Nebulizer: 20 mg/ampule	2 puffs four times daily 1 ampule four times daily	• 4- to 6-week trial may be needed to determine maximum benefit. • Dose by MDI may be inadequate to affect hyperresponsiveness. • One dose before exercise or allergen exposure provides effective prophylaxis for 1–2 hours. Not as effective for EIB as SABA. • Once control is achieved, the frequency of dosing may be reduced.
Nedocromil	MDI: 1.75 mg/puff	2 puffs four times daily	
Inhaled Long-Acting Anticholinergic			**Should not be used for symptom relief or exacerbations. Use with ICS.**
Tiotropium	DPI: 18 mcg/blister	1 blister daily	

(*continued*)

Table 9–2. Long-term controller medications for asthma. (continued)

Medication	Dosage Form	Adult Dose	Comments
Leukotriene Modifiers			
Leukotriene Receptor Antagonists			
Montelukast	4- or 5-mg chewable tablet; 10-mg tablet	10 mg daily at bedtime	• Exhibits a flat dose-response curve. Doses > 10 mg will not produce a greater response in adults.
Zafirlukast	10- or 20-mg tablet	20-mg tablet twice daily	• Administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. • Monitor for symptoms and signs of hepatic dysfunction.
5-Lipoxygenase Inhibitor			
Zileuton	600-mg tablet	600 mg four times daily	• Monitor hepatic enzyme (ALT).
Methylxanthines			
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose: 10 mg/kg/day up to 300 mg maximum Usual maximum dose: 800 mg/day	• Adjust dose to achieve serum concentration of 5–15 mcg/mL after at least 48 hours on same dose. • Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is important.
Monoclonal Antibodies			
Omalizumab	Subcutaneous injection	Dependent on pretreatment IgE level; up to 375 mg every 2 weeks	• Binds to IgE; prevents interaction with IgE receptor on mast cells and basophils. • Carries black-box warning of anaphylaxis. • Suggested IgE level 30–1500 IU/mL.
Mepolizumab	Subcutaneous injection	100 mg every 4 weeks	• Binds to IL-5; prevents interaction with receptor. • Suggested AEC ≥ 150–300/mcL ($0.15–0.3 \times 10^9$/L).
Reslizumab	Intravenous injection	3 mg/kg every 4 weeks	• Binds to IL-5; prevents interaction with receptor. • Carries black-box warning of anaphylaxis. • Suggested AEC ≥ 400/mcL (0.4×10^9/L).
Benralizumab	Subcutaneous injection	30 mg every 4 weeks for 3 doses, then every 8 weeks	• Binds to IL-5 receptor; blocks receptor-ligand interaction and also causes apoptosis of basophils and eosinophils. • Suggested AEC ≥ 300/mcL (0.3×10^9/L).
Dupilumab	Subcutaneous injection	200 or 300 mg every 2 weeks	• Binds to IL-4Ralpha; blocks IL-4 and IL-13 signaling. • Suggested AEC ≥ 150/mcL (0.15×10^9/L) and/or FENO ≥ 25 ppb.

AEC, absolute eosinophil count; DPI, dry powder inhaler; EIB, exercise-induced bronchospasm; FENO, fractional exhaled nitric oxide; HFA, hydrofluoroalkane; LABA, long-acting beta-2-agonist; MDI, metered-dose inhaler; SABA, short-acting beta-2-agonist.

SABA from an MDI are usually sufficient for mild to moderate symptoms. Severe exacerbations frequently require higher doses: 6–12 puffs every 30–60 minutes of albuterol by MDI with an inhalation chamber or 2.5 mg by nebulizer provide equivalent bronchodilation. Administration by nebulization does not offer more effective delivery than MDIs used correctly but does provide higher doses. With most SABAs, the recommended dose by nebulizer for acute asthma (albuterol, 2.5 mg) is 25–30 times that delivered by a single activation of the MDI (albuterol, 0.09 mg). This difference suggests that standard dosing of inhalations from an MDI may be insufficient in the setting of an acute exacerbation. Independent of dose, nebulizer therapy may be more effective in patients who are unable to coordinate inhalation of medication from an MDI because of age, agitation, or severity of the exacerbation.

Table 9–3. Reliever medications for asthma.

Medication	Dosage Form	Adult Dose	Comments
Inhaled Short-Acting Beta-2-Agonists (SABA)			
Albuterol CFC	MDI: 90 mcg/puff, 200 puffs/canister	2 puffs 5 minutes before exercise 2 puffs every 4–6 hours as needed	• An increasing use or lack of expected effect indicates diminished control of asthma. • Not recommended for long-term daily treatment. Regular use exceeding 2 days/week for symptom control (not prevention of EIB) indicates the need to step up therapy. • Differences in potency exist, but all products are essentially comparable on a per-puff basis. • May double usual dose for mild exacerbations. • Prime the inhaler by releasing four actuations prior to use. • Periodically clean HFA activator, as drug may block/plug orifice.
Albuterol HFA	MDI: 90 mcg/puff, 200 puffs/canister	2 puffs 5 minutes before exercise 2 puffs every 4–6 hours as needed	
Pirbuterol CFC	MDI: 200 mcg/puff, 400 puffs/canister	2 puffs 5 minutes before exercise 2 puffs every 4–6 hours as needed	
Levalbuterol HFA	MDI: 45 mcg/puff, 200 puffs/canister	2 puffs 5 minutes before exercise 2 puffs every 4–6 hours as needed	
Albuterol	Nebulizer solution: 0.63 mg/3 mL 1.25 mg/3 mL 2.5 mg/3 mL 5 mg/mL (0.5%)	1.25–5 mg in 3 mL of saline every 4–8 hours as needed	• May mix with budesonide inhalant suspension, cromolyn, or ipratropium nebulizer solutions. • May double dose for severe exacerbations.
Levalbuterol (R-albuterol)	Nebulizer solution: 0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/0.5 mL 1.25 mg/3 mL	0.63–1.25 mg every 8 hours as needed	• Compatible with budesonide inhalant suspension. The product is a sterile-filled, preservative-free, unit dose vial.
Anticholinergics			
Ipratropium HFA	MDI: 17 mcg/puff, 200 puffs/canister	2–3 puffs every 6 hours	• Evidence is lacking for anticholinergics producing added benefit to beta-2-agonists in long-term asthma control therapy.
	Nebulizer solution: 0.25 mg/mL (0.025%)	0.25 mg every 6 hours	
Ipratropium with albuterol	MDI: 18 mcg/puff of ipratropium bromide and 90 mcg/puff of albuterol, 200 puffs/canister	2–3 puffs every 6 hours	
	Nebulizer solution: 0.5 mg/3 mL ipratropium bromide and 2.5 mg/3 mL albuterol	3 mL every 4–6 hours	• Contains EDTA to prevent discolorations of the solution. This additive does not induce bronchospasm.
Systemic Corticosteroids			
Methylprednisolone	2-, 4-, 6-, 8-, 16-, 32-mg tablets	40–60 mg/day as single or 2 divided doses	• Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. • The burst should be continued until symptoms resolve and the PEF is at least 80% of personal best. This usually requires 3–10 days but may require longer. There is no evidence that tapering the dose following improvements prevents relapse.
Prednisolone	5-mg tablets; 5 mg/5 mL, 15 mg/5 mL oral solution	40–60 mg/day as single or 2 divided doses	

(*continued*)

Table 9–3. Reliever medications for asthma. (continued)

Medication	Dosage Form	Adult Dose	Comments
Prednisone	1-, 2.5-, 5-, 10-, 20-, 50-mg tablets; 5 mg/mL oral solution	40–60 mg/day as single or 2 divided doses	
Methylprednisolone acetate	Repository injection: 40 mg/mL 80 mg/mL	240 mg intramuscularly once	• May be used in place of a short burst of oral corticosteroids in patients who are vomiting or if adherence is a problem.

CFC, chlorofluorocarbon; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; PEF, peak expiratory flow.
Adapted from National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Pub. No. 08-4051. Bethesda, MD, 2007.

GINA does not recommend SABA-only treatment of asthma in adults or adolescents and does not recommend scheduled daily use of SABAs. Although SABA is effective as a quick relief medication, patients who are treated with SABA alone are at increased risk for asthma-related death and urgent health care even if their symptoms are controlled. Increased use (more than one canister a month) or lack of expected effect indicates diminished asthma control and the need for additional long-term controller therapy.

LABAs provide bronchodilation for up to 12 hours after a single dose. Salmeterol and formoterol are LABAs available for asthma in the United States. In combination with an inhaled corticosteroid they are indicated for long-term prevention of asthma symptoms (including nocturnal symptoms) and for prevention of exercise-induced bronchospasm. LABAs should not be used as monotherapy because they have no anti-inflammatory effect and because monotherapy has been associated with a small but

Table 9–4. Estimated clinically comparable daily dosages for inhaled corticosteroids for adults with asthma.

Medication	Low Daily Dose	Medium Daily Dose	High Daily Dose
Beclomethasone dipropionate HFA 40 or 80 mcg/puff	80–240 mcg	> 240–480 mcg	> 480 mcg
Budesonide dipropionate DPI 90, 180, or 200 mcg/inhalation	180–400 mcg	> 400–800 mcg	> 800 mcg
Flunisolide 250 mcg/puff	500–1000 mcg	> 1000–2000 mcg	> 2000 mcg
Flunisolide HFA 80 mcg/puff	320 mcg	> 320–640 mcg	> 640 mcg
Fluticasone propionate **HFA/MDI:** 44, 110, or 220 mcg/puff **DPI:** 50, 100, or 250 mcg/inhalation	88–264 mcg 100–300 mcg	> 264–440 mcg > 300–500 mcg	> 440 mcg > 500 mcg
Mometasone furoate DPI 200 mcg/puff	200 mcg	400 mcg	> 400 mcg
Triamcinolone acetonide 75 mcg/puff	300–750 mcg	> 750–1500 mcg	> 1500 mcg

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler.
Notes:
- The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. Most of clinical benefit from inhaled corticosteroid therapy is seen at low doses; responsiveness varies among patients.
- Potential drug interactions: Several inhaled corticosteroids, including fluticasone, budesonide, and mometasone, are metabolized in the GI tract and liver by CYP 3A4 isoenzymes. Potent inhibitors of CYP 3A4, such as ritonavir and ketoconazole, have the potential for increasing systemic concentrations of these inhaled corticosteroids by increasing oral availability and decreasing systemic clearance. Some cases of clinically significant Cushing syndrome and secondary adrenal insufficiency have been reported.

Adapted from National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Pub. No. 08-4051. Bethesda, MD, 2007, and Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. (Available from: www.ginasthma.org.)

statistically significant increased risk of severe or fatal asthma attacks in two large studies. Combination inhalers containing formoterol and low-dose budesonide are the preferred option because of a large study in mild asthma that showed a 64% reduction in severe exacerbations compared with SABA-only treatment, and two large studies in mild asthma that showed noninferiority for severe exacerbations compared to low-dose inhaled corticosteroid alone.

3. Systemic corticosteroids—Systemic corticosteroids (oral prednisone or prednisolone or parenteral methylprednisolone) are most effective in achieving prompt control of asthma during acute exacerbations. Systemic corticosteroids are effective as primary treatments for patients with moderate to severe asthma exacerbations and for patients with exacerbations that do not respond promptly and completely to inhaled SABA therapy. These medications speed the resolution of airflow obstruction and reduce the rate of relapse. Delays in administering corticosteroids may result in progressive impairment. Therefore, patients with moderate to severe asthma should be prescribed oral corticosteroids so they are available for early, at-home administration. The minimal effective dose of systemic corticosteroids for asthma patients has not been identified. Outpatient prednisone "burst" therapy is 0.5–1 mg/kg/day (typically 40–60 mg) in 1–2 doses for 3–7 days. Severe exacerbations requiring hospitalization typically require 1 mg/kg of prednisone or methylprednisolone every 6–12 hours for 48 hours or until the FEV_1 (or PEF rate) returns to 50% of predicted (or 50% of baseline). The dose is then decreased to 0.5 mg/kg/day until the PEF reaches 70% of predicted or personal best. No clear advantage has been found for higher doses of corticosteroids. It may be prudent to administer corticosteroids intravenously to critically ill patients to avoid concerns about altered GI absorption.

In patients with refractory, poorly controlled asthma, systemic corticosteroids may be required for the long-term suppression of symptoms. Repeated efforts should be made to reduce the dose to the minimum needed to control symptoms. Concurrent treatment with calcium supplements and vitamin D should be initiated to prevent corticosteroid-induced bone mineral loss with long-term administration. Bone mineral density testing after 3 or more months of cumulative systemic corticosteroid exposure can guide the use of bisphosphonates for treatment of steroid-induced osteoporosis. Rapid discontinuation of systemic corticosteroids after long-term use may precipitate adrenal insufficiency.

4. Anticholinergics—Anticholinergic agents reverse vagally mediated bronchospasm but not allergen- or exercise-induced bronchospasm. They may decrease mucous gland hypersecretion. Both **short-acting muscarinic antagonists** (SAMAs) and **long-acting muscarinic antagonists** (LAMAs) are available. Ipratropium bromide, a SAMA, is less effective than SABA for relief of acute bronchospasm, but it is the inhaled drug of choice for patients with intolerance to SABA or with bronchospasm due to beta-blocker medications. Ipratropium bromide reduces the rate of hospital admissions when added to inhaled SABAs in patients with moderate to severe asthma exacerbations. Studies have shown that the addition of tiotropium to medium-dose inhaled corticosteroid and salmeterol improves lung function and reduces the frequency of asthma exacerbations.

5. Leukotriene modifiers—Leukotrienes are potent mediators that contribute to airway obstruction and asthma symptoms by contracting airway smooth muscle, increasing vascular permeability and mucous secretion, and attracting and activating airway inflammatory cells. **Zileuton** is a 5-lipoxygenase inhibitor that decreases leukotriene production, and **zafirlukast** and **montelukast** are cysteinyl leukotriene receptor antagonists. In randomized controlled trials (RCTs), these agents caused modest improvements in lung function and reductions in asthma symptoms and lessened the need for SABA rescue therapy. These agents are less effective than inhaled corticosteroid for exacerbation reduction but may be considered as alternatives in patients with asthma who are unable to take inhaled corticosteroid or who experience undesirable corticosteroid side effects.

6. Monoclonal antibody agents—Asthmatic patients who require monoclonal antibody therapies should be evaluated by either a pulmonologist or allergist experienced in their use. **Omalizumab** is a recombinant antibody that binds IgE without activating mast cells. Clinical trials in patients with moderate to severe asthma and elevated serum IgE levels have found that omalizumab, when administered subcutaneously every 2–4 weeks, reduced the need for corticosteroids. Three other IL-5 antagonist monoclonal antibodies (anti IL-5/5R) are approved for the treatment of severe asthma with peripheral blood eosinophilia that has not responded to standard treatments: **reslizumab** (administered intravenously every 4 weeks), **mepolizumab** (administered subcutaneously every 4 weeks), and **benralizumab** (administered subcutaneously every 4–8 weeks). **Dupilumab** is a monoclonal antibody (anti-IL-4Rα) that, when administered subcutaneously every 2 weeks, inhibits overactive signaling of IL-4 and IL-13.

7. Phosphodiesterase inhibitor—Theophylline provides mild bronchodilation in asthmatic patients. It also has anti-inflammatory and immunomodulatory properties, enhances mucociliary clearance, and strengthens diaphragmatic contractility. Sustained-release theophylline preparations are effective in controlling nocturnal symptoms and as added therapy in patients with moderate or severe persistent asthma whose symptoms are inadequately controlled by inhaled corticosteroids. Low-dose sustained-release theophylline is included as a less effective option in Step 3 treatment. Neither theophylline nor aminophylline is recommended for therapy of acute asthma exacerbations.

8. Mediator inhibitors—Cromolyn sodium and nedocromil are long-term control medications that prevent asthma symptoms and improve airway function in patients with mild persistent or exercise-induced asthma.

B. Desensitization

Immunotherapy for specific allergens may be considered in selected asthma patients who have exacerbations when exposed to allergens to which they are sensitive and when unresponsive to environmental control measures or other therapies. Studies show a reduction in asthma symptoms in patients treated with single-allergen immunotherapy. Because of the risk of immunotherapy-induced bronchoconstriction, it should be administered only in a setting where such complications can be immediately treated.

C. Vaccination

Adult patients aged 19–64 with asthma should receive the 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23) and annual influenza vaccinations as well as COVID-19 vaccination. Inactive vaccines (Pneumovax) are associated with few side effects. However, the use of the intranasal live attenuated influenza vaccine may be associated with asthma exacerbations in young children.

Treatment of Asthma Exacerbations

GINA asthma treatment algorithms begin with an assessment of the severity of a patient's baseline asthma. Adjustments to that algorithm follow a stepwise approach based on a careful assessment of asthma control. Educating patients to recognize symptoms of an exacerbation and to use their action plan are important aspects of asthma management. Symptoms of exacerbations include progressive breathlessness, increasing chest tightness, decreased peak flow, and lack of improvement after SABA therapy (Table 9–5). Most instances of uncontrolled asthma are mild and can be managed successfully by patients at home with self-management plans. More severe exacerbations require evaluation and management in a primary care office (Figure 9–2) or emergency department setting (Figure 9–3).

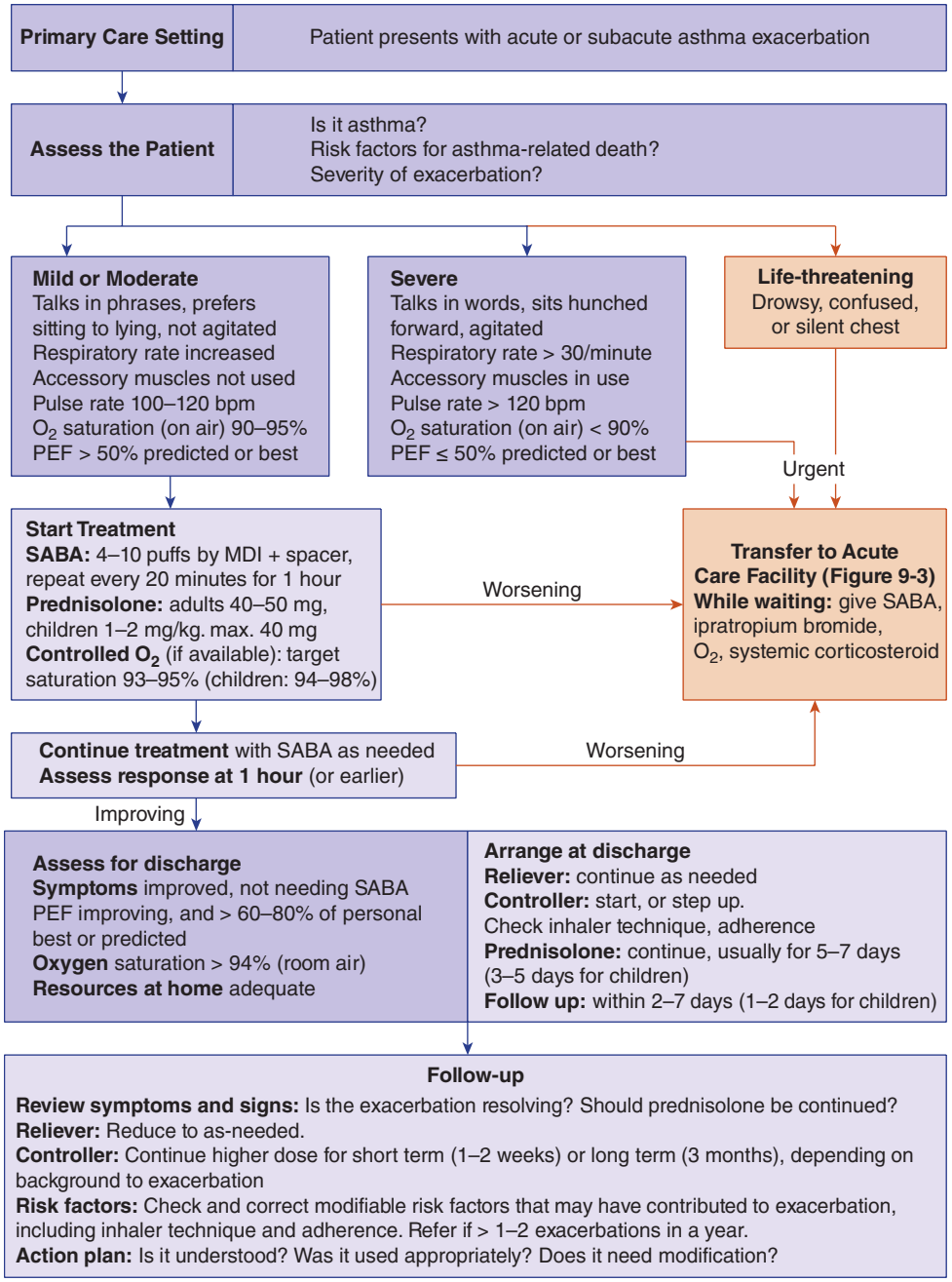
A. Mild to Moderate Exacerbations

Mild asthma exacerbations are characterized by only minor changes in airway function (PEF greater than 60% of best) with minimal symptoms and signs of airway dysfunction. Many such patients respond quickly and fully to an inhaled SABA alone. However, an inhaled SABA may need to be continued at increased doses, eg, every 3–4 hours for 24–48 hours. Patients may also require a short-term increase in inhaled corticosteroid to four times the usual dose. In patients not improving after 48 hours, a 5- to 7-day course

Table 9–5. Evaluation and classification of severity of asthma exacerbations.

	Mild	Moderate	Severe	Respiratory Arrest Imminent
Symptoms				
Breathlessness	While walking	At rest, limits activity	At rest, interferes with conversation	While at rest, mute
Talks in	Sentences	Phrases	Words	Silent
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Signs				
Respiratory rate	Increased	Increased	Often > 30/minute	> 30/minute
Body position	Can lie down	Prefers sitting	Sits upright	Unable to recline
Use of accessory muscles, suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheezing	Moderate, often only end expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absent
Pulse/minute	< 100	100–120	> 120	Bradycardia
Pulsus paradoxus	Absent < 10 mm Hg	May be present 10–25 mm Hg	Often present > 25 mm Hg	Absence suggests respiratory muscle fatigue
Functional Assessment				
PEF or FEV_1 % predicted or % personal best	≥ 70%	40–69%	< 40%	< 25%
Pao_2 (on air, mm Hg)	Normal[1]	≥ 60[1]	< 60: possible cyanosis	< 60: possible cyanosis
Pco_2 (mm Hg)	< 42[1]	< 42[1]	≥ 42[1]	≥ 42[1]
Sao_2 (on air)	> 95%[1]	90–95%[1]	< 90%[1]	< 90%[1]

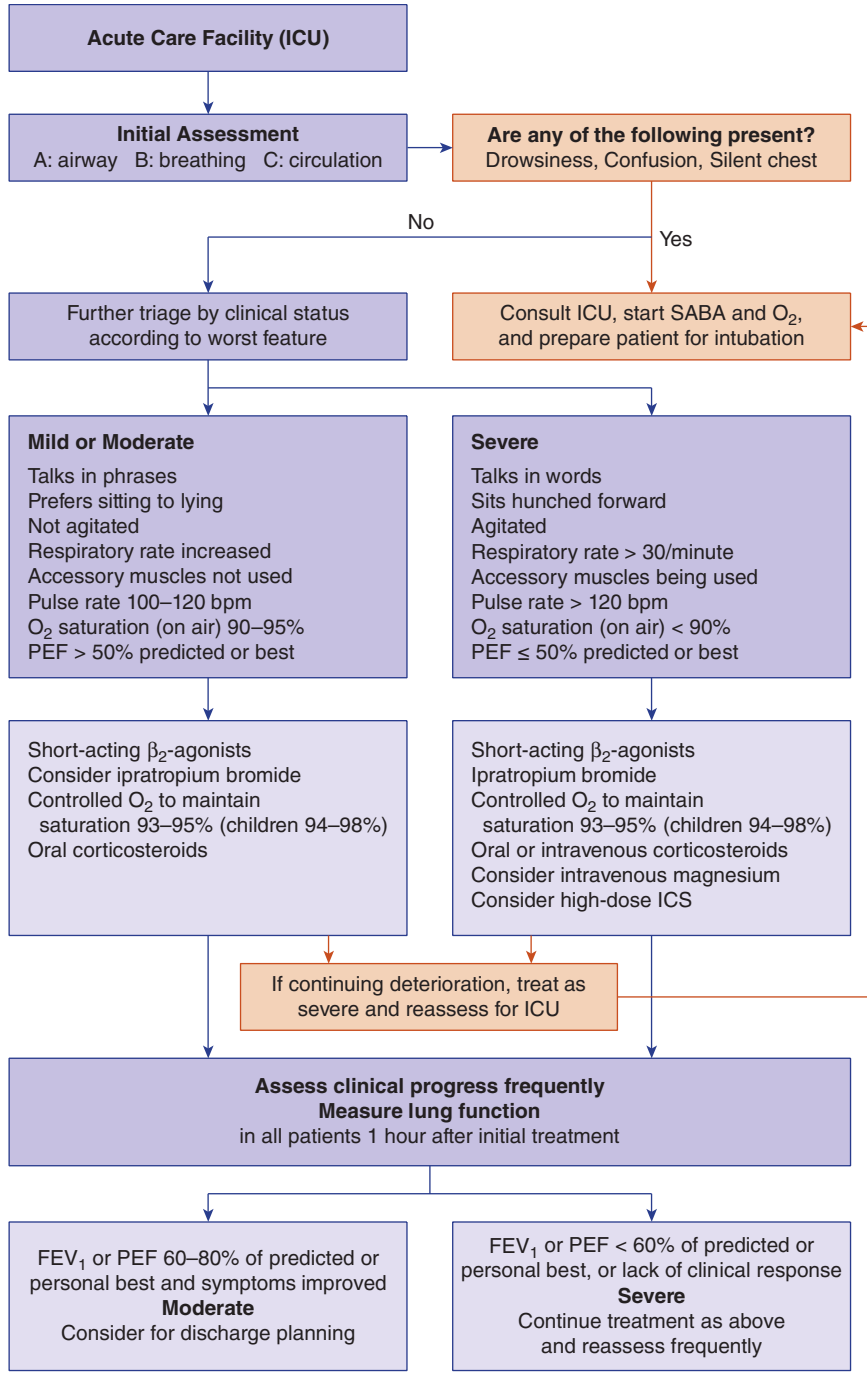
[1]Test not usually necessary.
FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow; Sao_2, oxygen saturation.
Adapted from National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Pub. No. 08-4051. Bethesda, MD, 2007.



▲ **Figure 9–2.** Management of asthma exacerbations in primary care. O_2, oxygen; PEF, peak expiratory flow; SABA, short-acting beta-2-agonist (doses are for salbutamol). (Reproduced with permission from Global Strategy for Asthma Management and Prevention (updated 2019). Global Initiative for Asthma-GINA, 2019.)

of oral corticosteroids (eg, prednisone 0.5–1.0 mg/kg/day) may be necessary.

The principal goals for treating moderate asthma exacerbations are correcting hypoxemia, reversing airflow obstruction, and reducing the likelihood of obstruction recurrence. Early intervention may lessen the severity and shorten the duration of an exacerbation. Airflow obstruction is treated with continuous administration of an **inhaled SABA** and the early administration of **systemic corticosteroids.** Systemic corticosteroids should be given to patients who have a peak flow less than 70% of baseline or who do not respond to several treatments of SABA. Serial measurements of lung function to quantify the severity of airflow obstruction and its response to treatment are useful. The improvement in FEV_1 after 30–60 minutes of treatment correlates significantly with the severity of the



▲ **Figure 9–3.** Management of asthma exacerbations in acute care facility (eg, emergency department). FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; O_2, oxygen; PEF, peak expiratory flow; SABA, short-acting beta-2-agonist. (Reproduced with permission from Global Strategy for Asthma Management and Prevention (updated 2019). Global Initiative for Asthma-GINA, 2019.)

asthma exacerbation. Serial measurement of airflow in the emergency department may reduce the rate of hospital admissions for asthma exacerbations. Post-exacerbation care planning is important. All patients, regardless of severity, should be provided with (1) necessary medications and how to use them, (2) instruction in self-assessment, (3) a follow-up appointment, and (4) an action plan for managing recurrence.

B. Severe Exacerbations

Severe exacerbations of asthma can be life-threatening, so treatment should be started immediately. All patients

with a severe exacerbation should immediately receive **oxygen,** high doses of an **inhaled SABA,** and **systemic corticosteroids.** A brief history pertinent to the exacerbation can be completed while such treatment is being initiated. More detailed assessments, including laboratory studies, usually add little early on and so should be postponed until after therapy is instituted. Early initiation of **oxygen therapy** is paramount because asphyxia is a common cause of asthma deaths. Supplemental oxygen should be given to maintain an Sao_2 greater than 90% or a Pao_2 greater than 60 mm Hg. Oxygen-induced hypoventilation is extremely rare in asthmatic patients, and concern for hypercapnia should never delay correction of hypoxemia.

Frequent high-dose delivery of an **inhaled SABA** is indicated and usually well tolerated in severe airway obstruction. At least three MDI or nebulizer treatments should be given in the first hour of therapy. Some studies suggest that continuous therapy is more effective than intermittent administration of these agents, but there is no clear consensus as long as similar doses are administered. After the first hour, the frequency of administration varies according to improvements in airflow and symptoms and occurrence of side effects. **Ipratropium bromide** reduces the rate of hospital admissions when added to inhaled SABAs in patients with moderate to severe asthma exacerbations.

Systemic corticosteroids are administered as detailed above. **Intravenous magnesium sulfate** (2 g intravenously over 20 minutes) is not recommended for routine use in asthma exacerbations. However, a 2 g infusion over 20 minutes may reduce hospitalization rates in acute severe asthma (FEV_1 less than 25% of predicted on presentation or failure to respond to initial treatment).

Mucolytic agents (eg, acetylcysteine, potassium iodide) may worsen cough or airflow obstruction. Anxiolytic and hypnotic drugs are generally contraindicated in severe asthma exacerbations because of their potential respiratory depressant effects.

Multiple studies suggest that infections with viruses (rhinovirus) and bacteria (*Mycoplasma pneumoniae, Chlamydophila pneumoniae*) predispose to acute exacerbations of asthma and may underlie chronic, severe asthma. The use of empiric antibiotics is, however, not recommended in routine asthma exacerbations since there is no consistent evidence to show improved clinical outcomes. **Antibiotics** should be considered when there is a high likelihood of acute bacterial respiratory tract infection, such as when patients have fever or purulent sputum and evidence of pneumonia or bacterial sinusitis.

In the **emergency department setting,** repeat assessment of patients with severe exacerbations should be done after the initial dose of an inhaled SABA and again after 3 doses of an inhaled SABA (60–90 minutes after initiating treatment). The response to initial treatment is a better predictor of the need for hospitalization than is the severity of the exacerbation on presentation. The decision to hospitalize a patient should be based on the duration and severity of symptoms, severity of airflow obstruction, ABG results (if available), course and severity of prior exacerbations, medication use at the time of the exacerbation, access to medical care and medications, adequacy of social support and home conditions, and presence of psychiatric illness. In general, discharge to home is appropriate if the PEF or FEV_1 has returned to 60% or more of predicted or personal best and if symptoms are minimal or absent. Patients with a rapid response to treatment should be observed for 30 minutes after the most recent dose of bronchodilator to ensure stability of response before discharge.

In the **intensive care setting,** a small subset of patients will not respond to treatment and will progress to impending respiratory failure due to a combination of worsening airflow obstruction and respiratory muscle fatigue (see Figure 9–3 and Table 9–5). Since such patients can deteriorate rapidly, they must be monitored in a critical care setting. Intubation of an acutely ill asthma patient is technically difficult and is best done semi-electively before the crisis of a respiratory arrest. At the time of intubation, the patient's intravascular volume should be closely monitored because hypotension commonly follows the administration of sedative medications and the initiation of positive-pressure ventilation; these patients are often dehydrated due to poor recent oral intake and high insensible losses.

The main goals of **mechanical ventilation** are to ensure adequate oxygenation and to avoid barotrauma. Controlled hypoventilation with permissive hypercapnia is often required to limit airway pressures. Frequent high-dose delivery of inhaled SABAs should be continued along with anti-inflammatory agents as discussed above.

When to Refer

- Atypical presentation or uncertain diagnosis of asthma, particularly if additional diagnostic testing is required (bronchoprovocation challenge, allergy skin testing, rhinoscopy, consideration of occupational exposure).
- Complicating comorbid problems, such as rhinosinusitis, tobacco use, multiple environmental allergies, suspected allergic bronchopulmonary aspergillosis.
- Occupational asthma.
- Uncontrolled symptoms despite a moderate-dose inhaled corticosteroid and a LABA.
- Patient not meeting goals of asthma therapy after 3–6 months of treatment.
- Frequent asthma-related health care utilization.
- More than two courses of oral corticosteroid therapy in the past 12 months.
- Any life-threatening asthma exacerbation or exacerbation requiring hospitalization in the past 12 months.
- Presence of social or psychological issues interfering with asthma management.

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE

ESSENTIALS OF DIAGNOSIS

- History of cigarette smoking or other chronic inhalational exposure.
- Chronic cough, dyspnea, and sputum production.
- Rhonchi, decreased intensity of breath sounds, and prolonged expiration on physical examination.
- Airflow limitation on PFT that is not fully reversible and is most often progressive.

General Considerations

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a common, preventable, and treatable disease state characterized by persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The term "COPD" has evolved from an umbrella term for chronic bronchitis and emphysema to one that refers to a clinical syndrome of chronic respiratory symptoms, structural pulmonary abnormalities (airways or alveoli), and impaired lung function arising from multiple causes that result in airflow limitation that is not fully reversible. Symptoms include cough, dyspnea, and sputum production. COPD is a major cause of chronic morbidity and is the third leading cause of death worldwide.

The most important causes of COPD are cigarette smoking in the developed world and biomass fuel cooking in the developing world. Most smokers suffer an accelerated decline in lung function that is dose- and duration-dependent. One major study of active smokers reported yearly decreases in FEV_1 of 66 mL per year in men and 54 mL per year in women compared to 30 mL per year in men and 22 mL per year in women who sustained smoking cessation. Fifteen percent of smokers develop progressively disabling symptoms in their 40s and 50s. Approximately two-thirds of patients seen for COPD have significant exposure to tobacco smoke. The remaining one-third may have a combination of exposures to environmental tobacco smoke, occupational dusts and chemicals, and indoor air pollution from biomass fuel used for cooking and heating in poorly ventilated buildings. Outdoor air pollution, airway infection, environmental factors, and allergy have also been implicated, along with hereditary factors (most notably, deficiency of alpha-1-antitrypsin [alpha-1-antiprotease]). Atopy and bronchoconstriction in response to nonspecific airway stimuli may be important risk factors. There is evidence that lung exposures to pollution and allergens early in life can lead to poor lung growth in childhood and expiratory airflow limitation, resulting in lower than predicted spirometric values in midlife.

Clinical Findings

A. Symptoms and Signs

Patients with COPD characteristically present in the fifth or sixth decade of life complaining of excessive cough, sputum production, or shortness of breath, or a combination thereof. Symptoms have often been present for 10 years or more, yet if diagnosed early, smoking cessation can reduce the decline in lung function. Dyspnea is noted initially only on heavy exertion, but as the condition progresses it occurs with mild activity. In severe disease, dyspnea occurs at rest. As the disease progresses, two symptom patterns tend to emerge, historically referred to as "pink puffers" and "blue bloaters" (Table 9–6). Most COPD patients have features of both disorders, and their clinical course and severity may involve other factors, such as central control of ventilation and concomitant sleep-disordered breathing.

A hallmark of COPD is the acute exacerbation of symptoms beyond normal day-to-day variation, often including increased dyspnea, an increased frequency or severity of cough, and increased sputum volume or change in sputum character. These exacerbations are commonly precipitated by infection (more often viral than bacterial) or environmental factors. Pneumonia, pulmonary hypertension, right-sided heart failure, and chronic respiratory failure characterize the late stage of COPD.

B. Laboratory Findings

Spirometry provides objective information about pulmonary function and assesses the response to therapy. PFTs early in the course of COPD may reveal only abnormal closing volume and reduced mid-expiratory flow rates. Reductions in FEV_1 and in the ratio of FEV_1 to vital capacity (FEV_1% or FEV_1/FVC ratio) establish the presence of airflow obstruction. In severe disease, the FVC is markedly reduced. Lung volume measurements reveal an increase in residual volume (RV) and in total lung capacity (TLC), and an elevation of the RV/TLC ratio, indicative of air trapping, particularly common in patients with emphysema. In the setting of airflow obstruction, a reduction in the single-breath diffusing capacity for carbon monoxide (DLCO) predicts emphysema. A severely reduced DLCO predicts exertional oxyhemoglobin desaturation and is associated with coexisting pulmonary hypertension. A 6-minute walking distance of less than 350 m is associated with increased mortality.

ABG measurement characteristically shows no abnormalities early in COPD other than an increased $A–a–Do_2$.

Table 9–6. Patterns of disease in advanced COPD.

	Type A: Pink Puffer (Emphysema Predominant)	Type B: Blue Bloater (Bronchitis Predominant)
History and physical examination	Major complaint is dyspnea, often severe, usually presenting after age 50. Cough is rare, with scant clear, mucoid sputum. Patients are thin, with recent weight loss common. They appear uncomfortable, with evident use of accessory muscles of respiration. Chest is very quiet without adventitious sounds. No peripheral edema.	Major complaint is chronic cough, productive of mucopurulent sputum, with frequent exacerbations due to chest infections. Often presents in late 30s and 40s. Dyspnea usually mild, though patients may note limitations to exercise. Patients frequently overweight and cyanotic but seem comfortable at rest. Peripheral edema is common. Chest is noisy, with rhonchi invariably present; wheezes are common.
Laboratory studies	Hemoglobin usually normal (12–15 g/dL). Pa_{O_2} normal to slightly reduced (65–75 mm Hg) but Sa_{O_2} normal at rest. Pa_{CO_2} normal to slightly reduced (35–40 mm Hg). Chest radiograph shows hyperinflation with flattened diaphragms. Vascular markings are diminished, particularly at the apices.	Hemoglobin usually elevated (15–18 g/dL). Pa_{O_2} reduced (45–60 mm Hg) and Pa_{CO_2} slightly to markedly elevated (50–60 mm Hg). Chest radiograph shows increased interstitial markings ("dirty lungs"), especially at bases. Diaphragms are not flattened.
Pulmonary function tests	Airflow obstruction ubiquitous. TLC increased, sometimes markedly so. DLCO reduced. Static lung compliance increased.	Airflow obstruction ubiquitous. TLC generally normal but may be slightly increased. DLCO normal. Static lung compliance normal.
Special Evaluations		
Ventilation-perfusion testing	Increased ventilation to high $\dot{V}/\dot{Q}$ areas, ie, high dead space ventilation.	Increased perfusion to low $\dot{V}/\dot{Q}$ areas.
Hemodynamics	Cardiac output normal to slightly low. Pulmonary artery pressures mildly elevated and increase with exercise.	Cardiac output normal. Pulmonary artery pressures elevated, sometimes markedly so, and worsen with exercise.
Nocturnal ventilation	Mild to moderate degree of oxygen desaturation not usually associated with obstructive sleep apnea.	Severe oxygen desaturation, frequently associated with obstructive sleep apnea.
Exercise ventilation	Increased minute ventilation for level of oxygen consumption; Pa_{O_2} tends to fall; Pa_{CO_2} rises slightly.	Decreased minute ventilation for level of oxygen consumption. Pa_{O_2} may rise; Pa_{CO_2} may rise significantly.

DLCO, single-breath diffusing capacity for carbon monoxide; TLC, total lung capacity; $\dot{V}/\dot{Q}$, ventilation-perfusion.

Indeed, ABG measurement is unnecessary unless (1) hypoxemia or hypercapnia is suspected, (2) the FEV_1 or DLCO is less than 40% of predicted, or (3) there are clinical signs of right heart failure. Hypoxemia occurs in advanced disease, particularly when chronic bronchitis predominates. Compensated respiratory acidosis occurs in patients with chronic respiratory failure, particularly in chronic bronchitis, with worsening of acidemia during acute exacerbations.

Positive sputum cultures are poorly correlated with acute exacerbations, and research techniques demonstrate evidence of preceding viral infection in most patients with exacerbations. The ECG may show sinus tachycardia, and in advanced disease, chronic pulmonary hypertension may produce electrocardiographic abnormalities typical of right-sided heart failure. Supraventricular arrhythmias (multifocal atrial tachycardia, atrial flutter, and atrial fibrillation) and ventricular irritability also occur.

C. Imaging

Radiographs of patients with chronic bronchitis typically show only nonspecific peribronchial and perivascular markings. Plain radiographs are insensitive for the diagnosis of emphysema; they show hyperinflation with flattening of the diaphragm or peripheral arterial deficiency in about half of cases. CT of the chest identifies and can quantify the emphysema phenotype associated with loss of tissue. Chest CT also detects airway narrowing and wall thickening characteristic of the bronchitic phenotype. In advanced disease, pulmonary hypertension may be suggested by enlargement of central pulmonary arteries on chest radiographs or chest CTs, and Doppler echocardiography provides an estimate of pulmonary artery pressure.

Differential Diagnosis

Clinical, imaging, and laboratory findings should enable the clinician to distinguish COPD from other obstructive pulmonary disorders, such as asthma, bronchiectasis, cystic fibrosis, bronchopulmonary aspergillosis, and central airflow obstruction. Asthma is characterized by complete or near-complete reversibility of airflow obstruction. Bronchiectasis is distinguished from COPD by recurrent pneumonia and hemoptysis, digital clubbing, and characteristic imaging abnormalities. Cystic fibrosis occurs in children, adolescents, and young adults and has characteristic imaging as well as endocrine and hepatic abnormalities. Bronchopulmonary aspergillosis is characterized by eosinophilia; elevated levels of immunoglobulin E; and episodic worsening marked by fever, malaise, productive cough, and radiographic infiltrates. Mechanical

obstruction of the central airways can be distinguished from COPD by flow-volume loops.

Complications

Acute bronchitis, pneumonia, pulmonary thromboembolism, atrial dysrhythmias (such as atrial fibrillation, atrial flutter, and multifocal atrial tachycardia), and concomitant LV failure may worsen otherwise stable COPD. Pulmonary hypertension, right-sided heart failure, and chronic respiratory failure are common in advanced COPD. Spontaneous pneumothorax occurs in a small fraction of patients with emphysema. Hemoptysis may result from chronic bronchitis or may signal bronchogenic carcinoma.

Prevention

COPD is largely preventable by eliminating long-term exposure to tobacco smoke, products of biomass fuels combustion, or other inhaled toxins. Smokers with early evidence of airflow limitation can significantly alter the course of their disease by smoking cessation. Influenza vaccination reduces the frequency and severity of influenza-like illness as well as the number of COPD exacerbations. Pneumococcal vaccination appears to reduce both the frequency of community-acquired pneumonia and the number of COPD exacerbations. COVID-19 vaccination reduces mortality.

Treatment

The treatment of COPD is guided by the severity of symptoms or the presence of an exacerbation of stable symptoms. Standards for the management of patients with stable COPD and COPD exacerbations from the American Thoracic Society and GOLD, a joint expert committee of the National Heart, Lung, and Blood Institute and the WHO, are incorporated in the recommendations below. There are three commonly used ways to identify high-risk COPD patients who may require more intense treatment: (1) FEV_1 less than 50% predicted, (2) more than two exacerbations in the previous year, and (3) one or more hospitalizations for COPD exacerbation in the previous year.

A. Ambulatory Patients

1. Smoking cessation—The single most important intervention in smokers with COPD is to facilitate smoking cessation (see Chapter 1). Simply telling a patient to quit succeeds 5% of the time. Behavioral approaches, ranging from clinician advice to intensive group programs, may improve cessation rates. Pharmacologic therapy includes bupropion, nicotine replacement (transdermal patch, gum, lozenge, inhaler, or nasal spray), and varenicline (a partial agonist of nicotinic acetylcholine receptors). Combined pharmacotherapies (two forms of nicotine replacement, or nicotine replacement and bupropion), with or without behavioral approaches, have been recommended. Varenicline is effective but use has been limited by concerns about neuropsychiatric side effects. Electronic cigarettes are not recommended as a smoking cessation aid, due in part to concern for e-cigarette and vaping-associated lung injury (EVALI) (see below).

2. Oxygen therapy—Supplemental oxygen for patients with resting hypoxemia (Pao_2 < 56 mm Hg) is the only therapy with evidence of improvement in the natural history of COPD. Proven benefits of home oxygen therapy in hypoxemic patients include longer survival, reduced hospitalizations, and better quality of life. Survival in hypoxemic patients with COPD treated with supplemental oxygen therapy is directly proportional to the number of hours per day oxygen is administered: in hypoxemic COPD patients treated with continuous oxygen for 24 hours daily, the survival after 36 months is about 65%—significantly better than the survival rate of about 45% in those treated with only nocturnal oxygen. Oxygen by nasal prongs must be given for at least 15 hours a day unless therapy is specifically intended only for exercise or sleep. However, several studies of supplemental oxygen therapy showed no survival benefit in COPD patients with borderline low-normal resting oxygen levels (Pao_2 56–69 mm Hg). In a study of patients with stable COPD and resting or exercise-induced moderate desaturation, the prescription of long-term supplemental oxygen did not result in a longer time to first hospitalization or death than no long-term supplemental oxygen, nor did it provide sustained benefit in any other measured outcomes. Requirements for US Medicare coverage for a patient's home use of oxygen and oxygen equipment are listed in Table 9–7. ABG analysis is preferred over oximetry to guide initial oxygen therapy. Hypoxemic patients with pulmonary hypertension, chronic right-sided heart failure, erythrocytosis, impaired cognitive function, exercise intolerance, nocturnal restlessness, or morning headache are particularly likely to benefit from home oxygen therapy.

Table 9–7. Home oxygen therapy: requirements for Medicare coverage.[1]

Group I (any of the following):

1. $Pao_2 \leq 55$ mm Hg or $Sao_2 \leq 88\%$ taken while awake, at rest, breathing room air.
2. During sleep (prescription for nocturnal oxygen use only): $Pao_2 \leq 55$ mm Hg or $Sao_2 \leq 88\%$ for a patient whose awake, resting, room air Pao_2 is ≥ 56 mm Hg or $Sao_2 \geq 89\%$, *or* Decrease in $Pao_2 > 10$ mm Hg or decrease in $Sao_2 > 5\%$ associated with symptoms or signs reasonably attributed to hypoxemia (eg, impaired cognitive processes, nocturnal restlessness, insomnia).
3. During exercise (prescription for oxygen use only during exercise): $Pao_2 \leq 55$ mg Hg or $Sao_2 \leq 88\%$ taken during exercise for a patient whose awake, resting, room air Pao_2 is ≥ 56 mm Hg or $Sao_2 \geq 89\%$, *and* there is evidence that the use of supplemental oxygen during exercise improves the hypoxemia that was demonstrated during exercise while breathing room air.

Group II[2]:

Pao_2 = 56–59 mm Hg or Sao_2 = 89% if there is evidence of any of the following:

1. Dependent edema suggesting heart failure.
2. P pulmonale on ECG (P wave > 3 mm in standard leads II, III, or aVF).
3. Hematocrit > 56%.

[1]Centers for Medicare & Medicaid Services, 2003.

[2]Patients in this group must have a second oxygen test 3 months after the initial oxygen setup.

Home oxygen may be supplied by liquid oxygen systems, compressed gas cylinders, or oxygen concentrators. Most patients benefit from having both stationary and portable systems. For most patients, a flow rate of 1–3 L/minute achieves a Pao_2 greater than 55 mm Hg. Reservoir nasal cannulas or "pendants" and demand (pulse) oxygen delivery systems are available to conserve oxygen.

3. Inhaled bronchodilators—Bronchodilators do not alter the inexorable decline in lung function that is a hallmark of COPD, but they improve symptoms, exercise tolerance, FEV_1, and overall health status. Aggressiveness of bronchodilator therapy should be matched to the severity of the patient's disease. In patients who experience no symptomatic improvement, bronchodilators should be discontinued.

The most commonly prescribed short-acting bronchodilators are the SAMA **ipratropium bromide** and the SABAs (eg, albuterol/salbutamol), delivered by MDI or as an inhalation solution by nebulizer. Some clinicians prefer ipratropium as a first-line agent because of its longer duration of action and absence of sympathomimetic side effects. Some studies have suggested that ipratropium achieves superior bronchodilation in COPD patients. Typical doses are 2–4 puffs (36–72 mcg) every 6 hours. Other clinicians prefer SABAs because they are less expensive and have a more rapid onset of action, commonly leading to greater patient satisfaction. At maximal doses, beta-2-agonists have bronchodilator action equivalent to that of ipratropium but may cause tachycardia, tremor, or hypokalemia. There does not appear to be any advantage of scheduled use of SABAs compared with as-needed administration. There has been no consistent difference in efficacy demonstrated between SABAs and SAMAs. Using the SABAs and the SAMAs at submaximal doses leads to improved bronchodilation compared with either agent alone but does not improve dyspnea.

LAMAs (eg, **tiotropium, aclidinium, umeclidinium, glycopyrrolate**) and LABAs (eg, **formoterol, salmeterol, indacaterol, arformoterol, vilanterol, olodaterol**) appear to achieve bronchodilation that is equivalent or superior to what is experienced with ipratropium, in addition to similar improvements in health status. Although more expensive than short-acting agents, long-acting bronchodilators may have superior clinical efficacy in persons with advanced disease. One RCT of long-term administration of **tiotropium** added to standard therapy reported fewer exacerbations or hospitalizations and improved dyspnea scores—but no long-term effect on lung function—in the tiotropium group. Another RCT comparing the effects of tiotropium with those of salmeterol-fluticasone over 2 years reported no difference in the risk of COPD exacerbation. The incidence of pneumonia was higher in the salmeterol-fluticasone group, yet dyspnea scores were lower and there was a mortality benefit compared with tiotropium. The combination of tiotropium and formoterol (LAMA/LABA) has been shown to improve FEV_1 and FVC more than the inhaled corticosteroid/LABA combination salmeterol and fluticasone in patients with a baseline FEV_1 of less than 55% predicted. The initial drug of choice for patients with mild disease and no exacerbations is a LAMA. If the patient has more severe dyspnea and airflow obstruction, LAMA/LABA can be initiated.

The symptomatic benefits of long-acting bronchodilators are firmly established. Increased exacerbations and mortality reported in some asthmatic patients treated with salmeterol have not been observed in COPD patients, and several studies report a trend toward lower mortality in patients treated with salmeterol alone, compared with placebo. In addition, a 4-year tiotropium trial reported fewer cardiovascular events in the intervention group. Subsequent meta-analyses that include the 4-year tiotropium trial did not find an increase in cardiovascular events in treated patients. Most practitioners believe that the documented benefits of anticholinergic therapy outweigh any potential risks.

4. Corticosteroids—Multiple large clinical trials have reported a reduction in the frequency of COPD exacerbations and an increase in self-reported functional status in COPD patients treated with inhaled corticosteroids. These same trials demonstrate no effect of inhaled corticosteroids on mortality or the characteristic decline in lung function experienced by COPD patients. Thus, inhaled corticosteroids alone should not be considered first-line therapy in stable COPD patients.

Three large clinical trials of combination therapy with an inhaled corticosteroid added to a LABA demonstrated a reduced frequency of exacerbations and modest improvements in lung function. The benefits of inhaled corticosteroids must be weighed against the increased risk of bacterial pneumonia, however (relative risk was increased 1.57-fold in one study). Withdrawal of inhaled corticosteroids should be considered when patients have been stable for 2 years.

Apart from acute exacerbations, COPD is not generally responsive to oral corticosteroid therapy. Given the risks of adverse side effects, oral corticosteroids are not recommended for long-term treatment of COPD.

5. Theophylline—Oral theophylline is a fourth-line agent for treating COPD patients who do not achieve adequate symptom control with inhaled anticholinergic, beta-2-agonist, and corticosteroid therapies. Theophylline improves dyspnea ratings, exercise performance, and pulmonary function in many patients with stable COPD. Its benefits result from bronchodilation; anti-inflammatory properties; and extrapulmonary effects on diaphragm strength, myocardial contractility, and kidney function. Theophylline toxicity is a significant concern due to the medication's narrow therapeutic window, and long-term administration requires careful monitoring of serum levels. GOLD guidelines recommend theophylline only as a last resort if other bronchodilators are unavailable or unaffordable.

6. Antibiotics—Antibiotics are commonly prescribed to outpatients with COPD for the following indications: (1) to treat an acute exacerbation, (2) to treat acute bronchitis, and (3) to prevent acute exacerbations of chronic bronchitis (prophylactic antibiotics). In patients with COPD, antibiotics appear to improve outcomes slightly in all three situations. Patients with a COPD exacerbation associated

with increased sputum purulence accompanied by dyspnea or an increase in the quantity of sputum are thought to benefit the most from antibiotic therapy. The choice of antibiotic depends on local bacterial resistance patterns and individual risk of *Pseudomonas aeruginosa* infection (history of *Pseudomonas* isolation, FEV_1 less than 50% of predicted, recent hospitalization [2 or more days in the past 3 months], more than three courses of antibiotics within the past year, use of systemic corticosteroids). Oral antibiotic options include doxycycline (100 mg every 12 hours), trimethoprim-sulfamethoxazole (160/800 mg every 12 hours), a cephalosporin (eg, cefpodoxime 200 mg every 12 hours or cefprozil 500 mg every 12 hours), a macrolide (eg, azithromycin 500 mg followed by 250 mg daily for 5 days), a fluoroquinolone (eg, ciprofloxacin 500 mg every 12 hours), and amoxicillin-clavulanate (875/125 mg every 12 hours). Suggested duration of therapy is 3–5 days and depends on response to therapy. There are few controlled trials of antibiotics in severe COPD exacerbations, but prompt administration is appropriate, particularly in persons with risk factors for poor outcomes (age older than 65 years, FEV_1 less than 50% of predicted, three or more exacerbations in the past year, antibiotic therapy within the past 3 months, comorbid conditions, such as cardiac disease). In COPD patients subject to frequent exacerbations despite optimal medical therapy, azithromycin (daily or three times weekly) and moxifloxacin (a 5-day course 1 week in 8 over 48 weeks) were modestly effective in clinical trials at reducing the frequency of exacerbations; monitoring for hearing loss and QT prolongation is essential.

7. Pulmonary rehabilitation—Graded aerobic physical exercise programs (eg, walking 20 minutes three times weekly or bicycling) are helpful to prevent deterioration of physical condition and to improve patients' ability to carry out daily activities. Training of inspiratory muscles by inspiring against progressively larger resistive loads reduces dyspnea and improves exercise tolerance, health status, and respiratory muscle strength in some but not all patients. Pursed-lip breathing to slow the rate of breathing and abdominal breathing exercises to relieve fatigue of accessory muscles of respiration may reduce dyspnea in some patients. Many patients undergo these exercise and educational interventions in a structured rehabilitation program. Pulmonary rehabilitation has been shown in multiple studies to improve exercise capacity, decrease hospitalizations, and enhance quality of life. Referral to a comprehensive rehabilitation program is recommended in patients who have severe dyspnea, reduced quality of life, or frequent hospitalizations despite optimal medical therapy.

8. Phosphodiesterase type 4 inhibitor—Roflumilast has been shown to reduce exacerbation frequency in patients who have moderate or severe (FEV_1 less than 50% of predicted) COPD and chronic bronchitis, with frequent exacerbations, and who are taking LABA/inhaled corticosteroid with or without a LAMA.

9. Other measures—In patients with chronic bronchitis, increased mobilization of secretions may be accomplished through adequate systemic hydration, effective cough training methods, or the use of a handheld flutter device and postural drainage, sometimes with chest percussion or vibration. Postural drainage and chest percussion should be used only in selected patients with excessive amounts of retained secretions that cannot be cleared by coughing and other methods; these measures are of no benefit in pure emphysema. Expectorant-mucolytic therapy has generally been regarded as unhelpful in patients with chronic bronchitis. Cough suppressants and sedatives should be avoided.

Human alpha-1-antitrypsin is available for replacement therapy in emphysema due to congenital deficiency (PiZZ or null genotype) of alpha-1-antitrypsin (alpha-1-antiprotease). Patients over 18 years of age with airflow obstruction by spirometry and serum levels less than 11 mmol/L (~50 mg/dL) are potential candidates for replacement therapy. Alpha-1-antitrypsin is administered intravenously in a dose of 60 mg/kg body weight once weekly.

Severe dyspnea despite optimal medical management may warrant a clinical trial of an **opioid** (eg, morphine 5–10 mg orally every 3–4 hours, oxycodone 5–10 mg orally every 4–6 hours, sustained-release morphine 10 mg orally once daily). Sedative-hypnotic drugs (eg, diazepam, 5 mg three times daily) marginally improve intractable dyspnea but cause significant drowsiness; they may benefit very anxious patients. Transnasal positive-pressure ventilation at home to rest the respiratory muscles is an approach to improve respiratory muscle function and reduce dyspnea in patients with severe COPD.

See Chapter 37 for a discussion of air travel in patients with lung disease.

B. Hospitalized Patients

Management of the hospitalized patient with an acute exacerbation of COPD includes (1) supplemental oxygen (titrated to maintain Sao_2 between 90% and 94% or Pao_2 between 60 mm Hg and 70 mm Hg); (2) inhaled beta-2-agonists (eg, albuterol 2.5 mg diluted with saline to a total of 3 mL by nebulizer, or MDI, 90 mcg per puff, four to eight puffs via spacer, every 1–4 hours as needed) with or without inhaled ipratropium bromide (500 mcg by nebulizer, or 36 mcg by MDI with spacer, every 4 hours as needed); (3) corticosteroids (prednisone 0.5 mg/kg/day orally for 7–10 days is usually sufficient, and even 5 days may be adequate); (4) broad-spectrum antibiotics; and (5) in selected cases, chest physiotherapy.

For patients without risk factors for *Pseudomonas*, management options include a fluoroquinolone (eg, levofloxacin 750 mg orally or intravenously per day, or moxifloxacin 400 mg orally or intravenously every 24 hours) or a third-generation cephalosporin (eg, ceftriaxone 1 g intravenously per day, or cefotaxime 1 g intravenously every 8 hours).

For patients with risk factors for *Pseudomonas*, therapeutic options include piperacillin-tazobactam (4.5 g intravenously every 6 hours), ceftazidime (1 g intravenously every 8 hours), cefepime (1 g intravenously every 12 hours), or levofloxacin (750 mg orally or intravenously per day for 3–7 days).

Oxygen therapy should *not* be withheld for fear of worsening respiratory acidemia; hypoxemia is more detrimental than hypercapnia. Right-sided heart failure usually responds to measures that reduce pulmonary artery pressure, such as supplemental oxygen and correction of acidemia; bed rest, salt restriction, and diuretics may add some benefit. Cardiac dysrhythmias, particularly multifocal atrial tachycardia, usually respond to aggressive treatment of COPD itself. Atrial fibrillation and flutter may require DC cardioversion after initiation of the above therapy. Theophylline should not be initiated in the acute setting, but patients taking theophylline prior to acute hospitalization should have their theophylline serum levels measured and maintained in the therapeutic range. If progressive respiratory failure ensues, tracheal intubation and mechanical ventilation are necessary. In clinical trials of COPD patients with hypercapnic acute respiratory failure, **noninvasive positive-pressure ventilation (NIPPV)** delivered via face mask reduced the need for intubation and shortened lengths of stay in the ICU. Other studies have suggested a lower risk of nosocomial infections and less use of antibiotics in COPD patients treated with NIPPV.

C. Procedures for COPD

1. Lung transplantation—Requirements for lung transplantation are severe lung disease, limited activities of daily living, exhaustion of medical therapy, ambulatory status, potential for pulmonary rehabilitation, limited life expectancy without transplantation, adequate function of other organ systems, and a good social support system. Two-year survival rate after lung transplantation for COPD is 75%. Complications include acute rejection, opportunistic infection, and obliterative bronchiolitis. Substantial improvements in pulmonary function and exercise performance have been noted after transplantation.

2. Lung volume reduction surgery—Lung volume reduction surgery, or reduction pneumoplasty, is a surgical approach to relieve dyspnea and improve exercise tolerance in patients with advanced diffuse emphysema and lung hyperinflation. Bilateral resection of 20–30% of lung volume in selected patients results in modest improvements in pulmonary function, exercise performance, and dyspnea. The duration of improvement as well as any mortality benefit remains uncertain. Prolonged air leaks occur in up to 50% of patients postoperatively. Mortality rates in centers with the largest experience with lung volume reduction surgery range from 4% to 10%.

The National Emphysema Treatment Trial compared lung volume reduction surgery with medical treatment in a randomized, multicenter clinical trial of 1218 patients with severe emphysema. Overall, surgery improved exercise capacity but not mortality when compared with medical therapy. The persistence of this benefit remains to be defined. Subgroup analysis suggested that patients with upper lobe–predominant emphysema and low exercise capacity might have improved survival, while other groups suffered excess mortality when randomized to surgery.

3. Bullectomy—Bullectomy is an older surgical procedure for palliation of dyspnea in patients with severe bullous emphysema. Bullectomy is most commonly pursued when a single bulla occupies at least 30–50% of the hemithorax.

Prognosis

The outlook for patients with clinically significant COPD is poor. The degree of pulmonary dysfunction at the time the patient is first seen is an important predictor of survival: median survival of patients with FEV_1 = 1 L or less is about 4 years. A multidimensional index (the BODE index), which includes **B**MI, airway **O**bstruction (FEV_1), **D**yspnea (modified Medical Research Council dyspnea score), and **E**xercise capacity, is a tool that predicts death and hospitalization better than FEV_1 alone. Comprehensive care programs, cessation of smoking, and supplemental oxygen may reduce the rate of decline of pulmonary function, but therapy with bronchodilators and other approaches probably have little, if any, impact on the natural course of COPD.

Dyspnea at the end of life can be extremely uncomfortable and distressing to the patient and family. As patients near the end of life, meticulous attention to palliative care is essential to effectively manage dyspnea (see Chapter 5).

When to Refer

- COPD onset occurs before the age of 40.
- Frequent exacerbations (two or more a year) despite optimal treatment.
- Severe or rapidly progressive COPD.
- Symptoms disproportionate to the severity of airflow obstruction.
- Need for long-term oxygen therapy.
- Onset of comorbid illnesses (eg, bronchiectasis, heart failure, or lung cancer).

When to Admit

- Severe symptoms or acute worsening that fails to respond to outpatient management.
- Acute or worsening hypoxemia, hypercapnia, peripheral edema, or change in mental status.
- Inadequate home care, or inability to sleep or maintain nutrition/hydration due to symptoms.
- The presence of high-risk comorbid conditions.

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BRONCHIECTASIS

ESSENTIALS OF DIAGNOSIS

- Chronic productive cough with dyspnea and wheezing.
- Radiographic findings of dilated, thickened airways and scattered, irregular opacities.

General Considerations

Bronchiectasis is a congenital or acquired disorder of the large bronchi characterized by permanent, abnormal dilation and destruction of bronchial walls. It may be caused by recurrent inflammation or infection of the airways and may be localized or diffuse. Cystic fibrosis causes about half of all cases of bronchiectasis. Other causes include lung infections (tuberculosis and nontuberculous mycobacteria, fungal infections, lung abscess, pneumonia), immunodeficiencies (congenital or acquired hypogammaglobulinemia; common variable immunodeficiency; selective IgA, IgM, and IgG subclass deficiencies; AIDS; lymphoma; plasma cell myeloma; leukemia), alpha-1-antitrypsin deficiency, primary ciliary dyskinesia, rheumatic diseases (rheumatoid arthritis, Sjögren syndrome); allergic bronchopulmonary aspergillosis (ABPA); and localized airway obstruction (foreign body, tumor, mucoid impaction).

Clinical Findings

A. Symptoms and Signs

Symptoms of bronchiectasis include chronic cough with production of copious amounts of purulent sputum, hemoptysis, pleuritic chest pain, dyspnea, and weight loss. Physical findings may include crackles at the lung bases and wheezing.

B. Laboratory Findings and Imaging

Laboratory tests include CBC with differential, immunoglobulin quantification; testing for cystic fibrosis with sweat chloride level; and sputum culture, including for nontuberculous mycobacteria. Additional testing, if appropriate, may include aspergillus antibodies, alpha-1-antitrypsin level, ciliary testing, autoimmune serologies, and swallow assessment. Obstructive pulmonary dysfunction with hypoxemia is seen in moderate or severe disease. High-resolution CT is the diagnostic study of choice. Radiographic abnormalities include dilated and thickened bronchi that may appear as "tram tracks" or as ring-like markings; scattered irregular opacities, atelectasis, and focal consolidation may be present.

C. Microbiology

Haemophilus influenzae is the most common organism recovered from non–cystic fibrosis patients with bronchiectasis. *P aeruginosa, Streptococcus pneumoniae*, and *Staphylococcus aureus* are commonly identified. Nontuberculous mycobacteria are seen less commonly. Patients with *Pseudomonas* infection experience an accelerated course, with more frequent exacerbations and more rapid decline in lung function.

Treatment

Treatment of acute exacerbations consists of antibiotics, daily chest physiotherapy with postural drainage and chest percussion, and inhaled bronchodilators. Handheld flutter valve devices may be as effective as chest physiotherapy in clearing secretions. Antibiotic therapy should be guided by sputum smears and prior cultures. If a specific bacterial pathogen cannot be isolated, then empiric oral antibiotic therapy for 10–14 days is appropriate. Common medications include amoxicillin or amoxicillin-clavulanate, ampicillin, a second- or third-generation cephalosporin, doxycycline, or a fluoroquinolone. For recurrent exacerbations, preventive macrolide therapy for 6–12 months has been found to decrease the frequency of exacerbations. Alternatively, inhaled antibiotics have been shown to reduce exacerbations. Alternating cycles of oral antibiotics may also be considered, although data are inconclusive.

Complications of bronchiectasis include hemoptysis, right-sided heart failure, amyloidosis, and secondary visceral abscesses at distant sites (eg, brain). Bronchoscopy is sometimes necessary to evaluate hemoptysis, remove retained secretions, and rule out obstructing airway lesions. Massive hemoptysis may require embolization of bronchial arteries or surgical resection.

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ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

ABPA is a pulmonary hypersensitivity disorder caused by allergy to fungal antigens that colonize the tracheobronchial tree. It usually occurs in atopic asthmatic individuals who are 20–40 years of age or those with cystic fibrosis, in response to antigens of *Aspergillus* species. Primary criteria for the diagnosis of ABPA include (1) a clinical history of asthma or cystic fibrosis; (2) elevated serum total IgE levels (greater than 1000 IU/mL); (3) immediate cutaneous hypersensitivity to *Aspergillus* antigens or elevated serum IgE levels specific to *Aspergillus fumigatus;* and (4) at least two of the following: (a) precipitating serum antibodies to *Aspergillus* antigen or elevated serum *Aspergillus* IgG by

immunoassay, (b) pulmonary radiographic abnormalities consistent with ABPA, or (c) peripheral blood eosinophil count greater than 500 cells/mcL (greater than 0.5×10^9/L). Radiographic abnormalities include transient opacities, mucoid impaction, and proximal or central bronchiectasis. High-dose corticosteroids (eg, prednisone 0.5–1 mg/kg orally per day) for at least 2 weeks with gradual taper is the treatment of choice. Patients with corticosteroid-dependent disease may benefit from itraconazole or voriconazole. Relapses are frequent. For those with frequent exacerbations, the use of biologic agents, such as anti-IgE (omalizumab), anti-IL-5 (mepolizumab, benralizumab), or anti-IL4 receptor (dupilumab), has been shown to improve outcomes. Bronchodilators (see Table 9–3) may also be helpful. Complications include hemoptysis, severe bronchiectasis, and pulmonary fibrosis.

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CYSTIC FIBROSIS

ESSENTIALS OF DIAGNOSIS

- Autosomal recessive disorder.
- Pulmonary disease: chronic or recurrent productive cough, dyspnea, and wheezing; recurrent airway infections or chronic colonization of the airways with *H influenzae, P aeruginosa, S aureus*, or *Burkholderia cenocepacia*; bronchiectasis and scarring on chest radiographs; airflow obstruction on spirometry.
- Extrapulmonary disease: sinus disease (chronic sinusitis and nasal polyposis); GI disease (pancreatic insufficiency, recurrent pancreatitis, hepatobiliary disease, meconium ileus, and distal intestinal obstruction); genitourinary problems (absent vas deferens and male infertility).
- Diagnosis: sweat chloride concentration > 60 mEq/L on two occasions; or presence of two disease-causing mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene; or sweat chloride concentration 30–59 mEq/L plus one disease-causing mutation in *CFTR* gene.

General Considerations

Cystic fibrosis is the most common cause of severe chronic lung disease in young adults and the most common fatal hereditary disorder of White persons in the United States. It is an autosomal-recessive disorder affecting about 1 in 3000 White persons; 1 in 25 is a carrier. Cystic fibrosis is caused by abnormalities in a membrane chloride channel (the cystic fibrosis transmembrane conductance regulator [CFTR] protein) that results in altered chloride transport and water flux across the apical surface of epithelial cells. Over 2000 different mutations of the *CFTR* gene have been identified with potential to cause disease. The most common mutation is ΔF508.

Clinical Findings

A. Symptoms and Signs

Cystic fibrosis should be suspected in an adult with a history of chronic lung disease (especially bronchiectasis), pancreatitis, or infertility. Cough, sputum production, decreased exercise tolerance, and recurrent hemoptysis are typical complaints. Patients also often complain of chronic rhinosinusitis symptoms, steatorrhea, diarrhea, and abdominal pain. Patients with cystic fibrosis are often malnourished with low BMI. Digital clubbing (Figure 6–42), increased anteroposterior chest diameter, hyperresonance to percussion, and apical crackles are noted on physical examination. Sinus tenderness, purulent nasal secretions, and nasal polyps may also be seen. Nearly all men with cystic fibrosis have congenital bilateral absence of the vas deferens with azoospermia. Biliary cirrhosis and gallstones may occur.

B. Laboratory Findings

ABG studies often reveal hypoxemia and, in advanced disease, a chronic, compensated respiratory acidosis. PFTs show a mixed obstructive and restrictive pattern. There is a reduction in FVC, airflow rates, and TLC. Air trapping (high ratio of RV to TLC) and reduction in pulmonary diffusing capacity are common.

C. Imaging

Hyperinflation is seen early in the disease process. Peribronchial cuffing, mucus plugging, bronchiectasis (ring shadows and cysts), increased interstitial markings, small rounded peripheral opacities, and focal atelectasis are common findings. Pneumothorax can also be seen. Thin-section CT scanning often confirms the presence of bronchiectasis.

D. Diagnosis

The **quantitative sweat test** reveals elevated sodium and chloride levels (greater than 60 mEq/L) in the sweat of patients with cystic fibrosis. Two tests on different days performed in experienced laboratories are required for accurate diagnosis. A normal sweat chloride test does not exclude the diagnosis, in which case *CFTR* genotyping or other alternative diagnostic studies (such as measurement of nasal membrane potential difference, semen analysis, or assessment of pancreatic function) should be pursued, especially if there is a high clinical suspicion of cystic fibrosis. Additionally, all patients with cystic fibrosis should undergo *CFTR* genotyping to determine whether they are eligible for CFTR modulator therapy.

Treatment

Early recognition and comprehensive multidisciplinary therapy improve symptom control and survival. Referral to a regional cystic fibrosis center is strongly recommended. Treatment programs focus on the following areas: CFTR modulator medications, clearance and reduction of lower airway secretions, reversal of bronchoconstriction, treatment of respiratory tract infections and airway bacterial burden, pancreatic enzyme replacement, and nutritional and psychosocial support (including genetic and occupational counseling).

CFTR modulators include medications that alter CFTR trafficking, folding, or function. These medications are only available for patients with specific *CFTR* mutations. Examples are **ivacaftor,** a potentiator of the CFTR channel that works by increasing the time the channel remains open after being activated; and **lumacaftor, tezacaftor,** and **elexacaftor**, which work by improving CFTR protein folding and cell-surface trafficking.

Airway clearance can be promoted by postural drainage, chest percussion or vibration techniques, positive expiratory pressure or flutter valve breathing devices, directed cough, and other breathing techniques. Inhaled **recombinant human deoxyribonuclease** (rhDNase, dornase alpha) cleaves extracellular DNA in sputum, decreasing sputum viscosity; when administered long-term at a daily nebulized dose of 2.5 mg, this therapy leads to improved FEV_1 and reduces the risk of cystic fibrosis–related respiratory exacerbations as well as the need for intravenous antibiotics. Inhalation of hypertonic (7%) saline improves clearance of mucus from the airway and has been associated with small improvements in pulmonary function and fewer pulmonary exacerbations.

Short-term antibiotics are used to treat active airway infections based on results of culture and susceptibility testing of sputum. *S aureus* (including methicillin-resistant strains) and a mucoid variant of *P aeruginosa* are commonly present. *H influenzae, Stenotrophomonas maltophilia*, and *B cenocepacia* (a highly drug-resistant organism) are occasionally isolated. **Long-term antibiotic therapy,** such as azithromycin (which has immunomodulatory properties) and various inhaled antibiotics (eg, tobramycin, aztreonam, colistin, and levofloxacin) taken two to three times a day, helps slow disease progression and reduce exacerbations in patients with sputum cultures positive for *P aeruginosa*. The length of therapy depends on the persistent presence of *P aeruginosa* in the sputum. The incidence of atypical mycobacterial colonization is higher in cystic fibrosis patients, and directed antibiotic treatment is recommended for frequent exacerbations, progressive decline in lung function, or failure to thrive.

Inhaled bronchodilators (eg, albuterol) should be considered in patients who demonstrate an increase of at least 12% in FEV_1 after an inhaled bronchodilator. An **inhaled corticosteroid** should be added to the treatment regimen for patients who have cystic fibrosis with persistent asthma or ABPA.

Lung transplantation is the only definitive treatment for advanced cystic fibrosis.

Vaccination against pneumococcal and coronavirus infections and annual influenza vaccination are advised. **Screening** of family members and genetic counseling are suggested.

Prognosis

The longevity of patients with cystic fibrosis is increasing. Death occurs from pulmonary complications (eg, pneumonia, pneumothorax, or hemoptysis) or as a result of terminal chronic respiratory failure and right-sided heart failure.

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BRONCHIOLITIS

ESSENTIALS OF DIAGNOSIS

- Insidious onset of cough and dyspnea.
- Irreversible airflow obstruction and air trapping on PFTs.
- Minimal findings on chest radiograph, heterogeneous airflow obstruction, and air trapping on chest CT scan.
- Relevant exposure or risk factors: toxic fumes, viral infections, organ transplantation, connective tissue disease.

General Considerations

Bronchiolitis is a generic term applied to varied inflammatory processes that affect the bronchioles, which are small conducting airways less than 2 mm in diameter. Bronchiolitis is less common in adults than in children, but it is encountered in multiple clinical settings, such as postinfectious, inhalational injury (such as vaping), organ transplantation, connective tissue diseases, and hypersensitivity pneumonitis.

The clinical approach to bronchiolitis divides patients into groups based on etiology, but different clinical syndromes may have identical histopathologic findings. As a result, no single classification scheme has been widely accepted, and there is an overlapping array of terms to describe these disorders from the viewpoints of the clinician, the pathologist, and the radiologist.

Clinical Findings

Acute bronchiolitis can be seen following viral infections.

Constrictive bronchiolitis (also referred to as obliterative bronchiolitis or bronchiolitis obliterans) is relatively infrequent, although it is the most common finding following inhalation injury (ammonia, welding fumes, and heavy metals). It may also be seen in rheumatoid arthritis; medication reactions (busulfan, gold, and penicillamine); and chronic rejection following heart-lung, lung, or hematopoietic stem cell transplantation (bronchiolitis obliterans syndrome). Patients with constrictive bronchiolitis have airflow obstruction and air trapping on spirometry; unremarkable plain chest radiographs but heterogeneous airflow obstruction and air trapping on chest CT scans; and a progressive, deteriorating clinical course.

Proliferative bronchiolitis (organizing pneumonia) is associated with diverse pulmonary disorders, including infection, aspiration, acute respiratory distress syndrome (ARDS), hypersensitivity pneumonitis, connective tissue diseases, and organ transplantation. Compared with constrictive bronchiolitis, proliferative bronchiolitis is more likely to have an abnormal chest radiograph. Chest CT scan may show patchy consolidation, ground-glass opacities, or peripheral nodular appearance. PFTs typically reveal a restrictive ventilatory defect and impaired oxygenation.

Follicular bronchiolitis is most commonly associated with connective tissue disease, especially rheumatoid arthritis and Sjögren syndrome, and with immunodeficiency states, such as HIV or common variable immunodeficiency. Chest CT scan may show centrilobular and peribronchial nodules. It may be seen in lymphoid interstitial pneumonia.

Respiratory bronchiolitis is the most common form of bronchiolitis in adults and is usually related to cigarette smoking. It usually occurs without symptoms or physiologic evidence of lung impairment. It may be seen in respiratory bronchiolitis–associated interstitial lung disease (RB-ILD). Chest CT may show centrilobular nodules, patchy ground-glass opacities, air trapping, and "tree-in-bud" opacities.

Diffuse panbronchiolitis is most frequently diagnosed in Japan. Men are affected about twice as often as women, two-thirds are nonsmokers, and most patients have a history of chronic pansinusitis. Patients complain of dyspnea, cough, and sputum production, and chest examination shows crackles and rhonchi. PFTs reveal obstructive abnormalities, and the chest radiograph shows a distinct pattern of diffuse, small, nodular shadows with hyperinflation.

Treatment

Constrictive bronchiolitis is relatively unresponsive to corticosteroids and is frequently progressive. Corticosteroids are usually effective in **proliferative bronchiolitis** and improvement can be prompt. Therapy is initiated with prednisone at 1 mg/kg/day orally for 1–3 months. The dose is then tapered slowly to 20–40 mg/day, depending on the response, and weaned over the subsequent 3–6 months as tolerated. Relapses are common if corticosteroids are stopped prematurely or tapered too quickly. Azithromycin may be used to effectively treat **diffuse panbronchiolitis** and, additionally, it may slow down the progression of bronchiolitis obliterans syndrome in lung transplant recipients.

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PULMONARY INFECTIONS

PNEUMONIA

Pneumonia has classically been considered in terms of the infecting organism (Table 9–8). This approach facilitates discussion of characteristic clinical presentations but is a limited guide to patient management since specific microbiologic information is usually not available at initial presentation. Current classification schemes emphasize epidemiologic factors that predict etiology and guide initial therapy. Pneumonia may be classified as **community-acquired pneumonia (CAP)** or **nosocomial pneumonia** and, within the latter, as **hospital-acquired pneumonia (HAP)** or **ventilator-associated pneumonia (VAP).** These categories are based on differing settings and infectious agents and require different diagnostic and therapeutic interventions. **Anaerobic pneumonia** and **lung abscess** can occur in both hospital and community settings.

This section sets forth the evaluation and management of pulmonary infiltrates in immunocompetent persons separately from the approach to immunocompromised persons—defined as those with HIV disease, absolute neutrophil counts less than 1000/mcL (1.0×10^9/L), or current or recent exposure to myelosuppressive or immunosuppressive medications.

1. Community-Acquired Pneumonia

ESSENTIALS OF DIAGNOSIS

- Fever or hypothermia, tachypnea, cough with or without sputum, dyspnea, chest discomfort, sweats or rigors (or both).
- Bronchial breath sounds, rhonchi, or inspiratory crackles on chest auscultation.
- Parenchymal opacity on chest radiograph (occasionally not evident at presentation).
- Occurs outside of the hospital or within 48 hours of hospital admission.

General Considerations

Community-acquired pneumonia (CAP) is a common disorder, with approximately 4–5 million cases diagnosed

Table 9–8. Characteristics of selected pneumonias.

Organism; Appearance on Smear of Sputum	Clinical Setting	Complications
Streptococcus pneumoniae (pneumococcus). Gram-positive diplococci.	Chronic cardiopulmonary disease; follows upper respiratory tract infection	Bacteremia, meningitis, endocarditis, pericarditis, empyema
Haemophilus influenzae. Pleomorphic gram-negative coccobacilli.	Chronic cardiopulmonary disease; follows upper respiratory tract infection	Empyema, endocarditis
Staphylococcus aureus. Plump gram-positive cocci in clumps.	Residence in long-term care facility, hospital-associated, influenza epidemics, cystic fibrosis, bronchiectasis, injection drug use	Empyema, cavitation
Klebsiella pneumoniae. Plump gram-negative encapsulated rods.	Alcohol abuse, diabetes mellitus; hospital-associated	Cavitation, empyema
Escherichia coli. Gram-negative rods.	Hospital-associated; rarely, community-acquired	Empyema
Pseudomonas aeruginosa. Gram-negative rods.	Hospital-associated; cystic fibrosis, bronchiectasis	Cavitation
Anaerobes. Mixed flora.	Aspiration, poor dental hygiene	Necrotizing pneumonia, abscess, empyema
Mycoplasma pneumoniae. PMNs and monocytes; no bacteria.	Young adults; summer and fall	Skin rashes, bullous myringitis; hemolytic anemia
Legionella species. Few PMNs; no bacteria.	Summer and fall; exposure to contaminated construction site, water source, air conditioner; community-acquired or hospital-associated	Empyema, cavitation, endocarditis, pericarditis
Chlamydophila pneumoniae. Nonspecific.	Clinically similar to *M pneumoniae*, but prodromal symptoms last longer (up to 2 weeks); sore throat with hoarseness common; mild pneumonia in teenagers and young adults	Reinfection in older adults with underlying COPD or heart failure may be severe or even fatal
Moraxella catarrhalis. Gram-negative diplococci.	Preexisting lung disease; elderly patients; corticosteroid or immunosuppressive therapy	Rarely, pleural effusions and bacteremia
Pneumocystis jirovecii. Nonspecific.	AIDS, immunosuppressive or cytotoxic drug therapy, cancer	Pneumothorax, respiratory failure, ARDS, death
SARS-CoV-2. Nonspecific.	Pandemic. Milder pneumonia (teenagers, young adults); more severe pneumonia (elderly, immunocompromised, multiple comorbidly ill adults)	Respiratory failure, ARDS, death

ARDS, acute respiratory distress syndrome; PMN, polymorphonuclear leukocyte; SARS-CoV-2, severe acute respiratory syndrome due to coronavirus-2 (see COVID-19 discussion, Chapter 32, and consult https://www.coronavirus.gov for the latest from the CDC).

each year in the United States, at least 25% of which require hospitalization. It is the deadliest infectious disease in the United States and is routinely among the top 10 causes of death. Mortality in milder cases treated as outpatients is less than 1%. Among patients hospitalized for CAP, in-hospital mortality is approximately 10–12% and 1-year mortality (in those over age 65) is greater than 40%. Risk factors for the development of CAP include older age; tobacco use; excessive alcohol use; comorbid medical conditions, especially COPD or other chronic lung disease; immunosuppression; and recent viral upper respiratory tract infection.

The patient's history, physical examination, and imaging studies are essential to establishing a diagnosis of CAP. None of these efforts identifies a specific microbiologic cause, however. Sputum examination may be helpful in selected patients but 40% of patients cannot produce an evaluable sputum sample; additionally, test characteristics of sputum Gram stain and culture vary by organism and lack sensitivity for some of the most common causes of pneumonia. Since patient outcomes improve when the initial antibiotic choice is appropriate for the infecting organism, the American Thoracic Society and the Infectious Diseases Society of America recommend empiric treatment based on epidemiologic data (Table 9–9). Such treatment improves initial antibiotic coverage, reduces unnecessary hospitalization, and appears to improve 30-day survival.

Definition & Pathogenesis

CAP is diagnosed outside of the hospital setting or within the first 48 hours of hospital admission. Pulmonary defense mechanisms (cough reflex, mucociliary clearance system, immune responses) normally prevent the development of lower respiratory tract infections following aspiration of oropharyngeal secretions containing bacteria or inhalation of infected aerosols. CAP occurs when there is a defect in

one or more of these normal defense mechanisms or when a large infectious inoculum or a virulent pathogen overwhelms the immune response.

Prospective studies fail to identify the cause of CAP in 30–60% of cases; two or more causes are identified in up to one-third of cases. The most common bacterial pathogen identified in most studies of CAP is *S pneumoniae*, accounting for approximately two-thirds of bacterial isolates. Other common bacterial pathogens include *H influenzae, M pneumoniae, C pneumoniae, S aureus, Moraxella catarrhalis, Klebsiella pneumoniae*, other gram-negative rods, and *Legionella* species. Common viral causes of CAP include coronaviruses (SARS-CoV-2, MERS), influenza virus, respiratory syncytial virus, adenovirus, and parainfluenza virus. A detailed assessment of epidemiologic risk factors may aid in diagnosing pneumonias due to the following uncommon causes: *Chlamydophila psittaci* (psittacosis); *Coxiella burnetii* (Q fever); *Francisella tularensis* (tularemia); *Blastomyces, Coccidioides, Histoplasma* (endemic fungi); and Sin Nombre virus (hantavirus pulmonary syndrome).

Clinical Findings

A. Symptoms and Signs

Most patients with CAP experience an acute or subacute onset of fever, cough with or without sputum production, and dyspnea. Other common symptoms include sweats, chills, rigors, chest discomfort, pleurisy, hemoptysis, fatigue, myalgias, anorexia, headache, and abdominal pain. Persons over age 80, however, may have an atypical presentation, including falls, delirium, lethargy, and anorexia.

Common physical findings include fever or hypothermia, tachypnea, tachycardia, and arterial oxygen desaturation. Many patients appear acutely ill. Chest examination often reveals inspiratory crackles, rhonchi, and bronchial breath sounds. Dullness to percussion may be observed if lobar consolidation or a parapneumonic pleural effusion is present. The clinical evaluation is less than 50% sensitive compared to chest imaging for the diagnosis of CAP (see Imaging section below). In most patients, therefore, a chest radiograph is essential to the evaluation of suspected CAP.

B. Diagnostic Testing

Diagnostic testing for a specific infectious cause of CAP is not generally indicated in ambulatory patients treated as outpatients because empiric antibiotic therapy is almost always effective in this population. In ambulatory outpatients whose presentation (travel history, exposure) suggests an etiology not covered by standard therapy (eg, *Coccidioides*) or public health concerns (eg, SARS-CoV-2, *Mycobacterium tuberculosis*, influenza), diagnostic testing is appropriate. Diagnostic testing is recommended in hospitalized CAP patients for multiple reasons: the likelihood of an infectious cause unresponsive to standard therapy is higher in more severe illness, the inpatient setting allows narrowing of antibiotic coverage as specific diagnostic information is available, and the yield of testing is improved in more acutely ill patients.

Diagnostic tests are used to adjust empirically chosen therapy and to facilitate epidemiologic analysis. Three widely available diagnostic tests may guide therapy: the sputum Gram stain and culture, urinary antigen tests for *S pneumoniae* and *Legionella* species, and tests for viruses such as influenza and SARS-CoV-2 (see COVID-19 discussion, Chapter 32). The usefulness of a sputum Gram stain lies in broadening initial coverage in patients to be hospitalized for CAP, most commonly to cover *S aureus* (including community-acquired methicillin-resistant *S aureus* [CA-MRSA] strains) or gram-negative rods (including *P aeruginosa* and Enterobacteriaceae). Urinary antigen assays for *Legionella pneumophila* and *S pneumoniae* are at least as sensitive and specific as sputum Gram stain and culture. Results of antigen testing are not affected by initiation of antibiotic therapy, and positive tests may allow narrowing of initial antibiotic coverage. Urinary antigen assay for *S pneumoniae* should be ordered for patients with leukopenia or asplenia or those with severe disease. Urinary antigen assay for *L pneumophila* should be ordered for patients in an area with an outbreak, with recent travel, with severe disease, or in whom a high clinical index of suspicion exists. Rapid influenza and SARS-CoV-2 testing has intermediate sensitivity but high specificity, with sensitivity depending on the method of detection (nucleic acid or PCR-based tests have higher sensitivity than antigen-based detection). Positive tests for viruses may reduce direct isolation of hospitalized patients but do not necessarily reduce the need for antibacterial therapy, since coinfection with a bacterial pathogen is common.

Rapid turnaround multiplex-PCR amplification from lower respiratory tract samples is increasingly available. Different commercial products can identify multiple strains of bacteria and viruses, in addition to genes that encode for antibiotic resistance. Early experience with multiplex-PCR shows improved overall diagnostic yield, particularly for viral infections, and a higher incidence of bacterial/viral coinfection than previously recognized. Limitations of multiplex-PCR include cost and availability, in addition to the challenge of interpreting potentially false-positive results from a highly sensitive test, since either viral or bacterial pathogens may colonize the airways.

Additional microbiologic testing including pre-antibiotic sputum and blood cultures (at least two sets with needle sticks at separate sites) has been standard practice for patients with CAP who require hospitalization. The yield of blood and sputum cultures is low, however; false-positive results are common, and the impact of culture results on patient outcomes is small. As a result, targeted testing is recommended for patients with severe disease and for those treated empirically for MRSA or *P aeruginosa* infection. The role of culture is to allow narrowing of initial empiric antibiotic coverage, adjustment of coverage based on specific antibiotic resistance patterns, to identify unsuspected pathogens not covered by initial therapy, and to provide information for epidemiologic analysis.

Apart from microbiologic testing, hospitalized patients should undergo CBC with differential and a chemistry panel (including serum glucose, electrolytes, BUN, creatinine, bilirubin, and liver enzymes). Hypoxemic patients

should have ABGs sampled. Test results help assess severity of illness and guide evaluation and management. HIV testing should be considered in all adult patients and performed in those with risk factors.

C. Imaging

A pulmonary opacity on chest radiography or CT scan is required to establish a diagnosis of CAP. Chest CT scan is more sensitive and specific than chest radiography and may be indicated in selected cases. Radiographic findings range from patchy airspace opacities to lobar consolidation with air bronchograms to diffuse alveolar or interstitial opacities. Additional findings can include pleural effusions and cavitation. Chest imaging cannot identify a specific microbiologic cause of CAP; no pattern of radiographic abnormalities is pathognomonic of any infectious cause.

Chest imaging may help assess severity and response to therapy over time. Progression of pulmonary opacities during antibiotic therapy or lack of radiographic improvement over time are poor prognostic signs and raise concerns about secondary or alternative pulmonary processes. Clearing of pulmonary opacities in patients with CAP can take 6 weeks or longer. Clearance is usually quickest in younger patients, nonsmokers, and those with only single-lobe involvement. Routine follow-up chest imaging is not indicated for most patients with CAP.

D. Special Examinations

Patients with CAP who have significant pleural fluid collections may require diagnostic thoracentesis (with pleural fluid sent for glucose, LD, and total protein levels; leukocyte count with differential; pH determination; and Gram stain and culture). Positive pleural cultures indicate the need for tube thoracostomy drainage.

Patients with cavitary opacities should have sputum fungal and mycobacterial cultures.

Sputum induction or fiberoptic bronchoscopy to obtain samples of lower respiratory secretions are indicated in patients with a worsening clinical course who cannot provide expectorated sputum samples or who may have pneumonia caused by *M tuberculosis* infection or certain opportunistic infections, including *Pneumocystis jirovecii.*

Differential Diagnosis

The differential diagnosis of lower respiratory tract infection is extensive and includes upper respiratory tract infections, reactive airway diseases, heart failure, interstitial pneumonias, lung cancer, pulmonary vasculitis, pulmonary thromboembolic disease, and atelectasis.

Treatment

Two general principles guide antibiotic therapy once the diagnosis of CAP is established: **prompt** initiation of a medication to which the etiologic pathogen is **susceptible.**

In patients who require specific diagnostic evaluation, sputum and blood culture specimens should be obtained prior to initiation of antibiotics. Since early administration of antibiotics to acutely ill patients is associated with improved outcomes, obtaining other diagnostic specimens or test results should not delay the initial dose of antibiotics.

Optimal antibiotic therapy would be pathogen directed, but a definitive microbiologic diagnosis is not typically available on presentation. A syndromic approach to therapy, based on clinical presentation and chest imaging, does not reliably predict the microbiology of CAP. Therefore, initial antibiotic choices are empiric, based on acuity (treatment as an outpatient, inpatient, or in the ICU), patient risk factors for specific pathogens, and local antibiotic resistance patterns (Table 9–9).

Since *S pneumoniae* remains a common cause of CAP in all patient groups, local prevalence of drug-resistant *S pneumoniae* significantly affects initial antibiotic choice. Prior treatment with one antibiotic in a pharmacologic class (eg, beta-lactam, macrolide, fluoroquinolone) predisposes to the emergence of drug-resistant *S pneumoniae*, with resistance developing against that class of antibiotics to which the pathogen was previously exposed. Definitions of resistance have shifted based on observations of continued clinical efficacy at achievable serum levels. In CAP, for parenteral penicillin G or oral amoxicillin, susceptible strains have a minimum inhibitory concentration (MIC) of 2 mcg/mL or less; intermediate resistance is defined as an MIC between 2 mcg/mL and 4 mcg/mL because treatment failures are uncommon with MIC of 4 mcg/mL or less. Macrolide resistance has increased; approximately one-third of *S pneumoniae* isolates now show in vitro resistance to macrolides. Treatment failures have been reported but remain rare compared to the number of patients treated. Current in vivo efficacy appears to justify maintaining macrolides as first-line therapy except in areas where there is a high prevalence of resistant strains. *S pneumoniae* resistance to fluoroquinolones is rare in the United States but is increasing.

CA-MRSA is genetically and phenotypically different from hospital-acquired MRSA strains. CA-MRSA is a rare cause of necrotizing pneumonia, empyema, respiratory failure, and shock; it appears to be associated with prior influenza infection. Linezolid may be preferred to vancomycin in treatment of CA-MRSA pulmonary infection. Daptomycin should **not** be used in any MRSA pneumonia because it does not achieve adequate concentration in the lung. For expanded discussions of specific antibiotics, see Chapters 30 and e1.

A. Treatment of Outpatients

See Table 9–9 for specific medication dosages. The most common etiologies of CAP in outpatients who do not require hospitalization are *S pneumoniae*; *M pneumoniae; C pneumoniae;* and respiratory viruses, including influenza. For previously healthy patients with no recent (90 days) use of antibiotics, the recommended treatment is a macrolide (clarithromycin or azithromycin), doxycycline, or amoxicillin. In areas with a high incidence of macrolide-resistant *S pneumoniae*, initial therapy in patients with no comorbidities may include the combination of a beta-lactam *plus* a macrolide, or a respiratory fluoroquinolone.

Table 9–9. Recommended empiric antibiotics for community-acquired bacterial pneumonia.

Outpatient management

1. For previously healthy patients with no risk factors for MRSA or *Pseudomonas*:
   a. Amoxicillin, 1 g orally three times daily, *or*
   b. Doxycycline, 100 mg orally twice a day, *or*
   c. In regions with a low rate (< 25%) of infection with high level (MIC ≥ 16 mcg/mL) macrolide-resistant *Streptococcus pneumoniae*, then a macrolide (clarithromycin, 500 mg orally twice a day; or azithromycin, 500 mg orally as a first dose and then 250 mg orally daily for 4 days, or 500 mg orally daily for 3 days).
2. For patients with comorbid medical conditions such as chronic heart, lung, liver, or kidney disease; diabetes mellitus; alcohol use disorder; malignancy; asplenia; immunosuppressant conditions or use of immunosuppressive drugs; or use of antibiotics within the previous 3 months (in which case an agent from a different antibiotic class should be selected):
   a. A macrolide *or* doxycycline (as above) *plus* an oral beta-lactam (amoxicillin/clavulanate 500 mg/125 mg three times daily, amoxicillin/clavulanate 875 mg/125 mg twice daily, amoxicillin/clavulanate 2 g/125 mg twice daily; cefpodoxime, 200 mg twice daily; cefuroxime, 500 mg twice daily).
   b. Monotherapy with an oral fluoroquinolone (moxifloxacin, 400 mg daily; gemifloxacin, 320 mg daily; levofloxacin, 750 mg daily).

Inpatient management of nonsevere pneumonia (typically not requiring intensive care)

1. A respiratory fluoroquinolone. Oral and intravenous doses equivalent: moxifloxacin, 400 mg daily or levofloxacin, 500–750 mg daily *or*
2. A macrolide (see above for oral therapy) *plus* a beta-lactam (see above for oral beta-lactam therapy). For intravenous therapy: ampicillin/sulbactam, 1.5–3 g every 6 hours; cefotaxime, 1–2 g every 8 hours; ceftriaxone, 1–2 g every 12–24 hours; ceftaroline, 600 mg every 12 hours.
3. For patients with prior respiratory isolation of MRSA, strongly consider adding coverage for MRSA and obtain cultures or nasal PCR to confirm infection or to allow de-escalation of therapy: vancomycin, typically starting at 15 mg/kg intravenously every 12 hours with interval dosing based on kidney function to achieve serum trough concentration 15–20 mcg/mL *or* linezolid, 600 mg orally or intravenously every 12 hours.
4. For patients with prior respiratory isolation of *Pseudomonas aeruginosa,* strongly consider adding coverage for *P aeruginosa* and obtain cultures to confirm infection or to allow de-escalation of therapy. Intravenous therapy only: piperacillin-tazobactam, 3.375–4.5 g every 6 hours; cefepime, 1–2 g every 8 hours; imipenem, 0.5–1 g every 6 hours; meropenem, 1 g every 8 hours; or aztreonam 2 g every 8 hours.

Inpatient management of severe pneumonia (typically requiring intensive care). All agents administered intravenously, except as noted.

1. Azithromycin (500 mg orally as a first dose and then 250 mg orally daily for 4 days, or 500 mg orally daily for 3 days) *or* a respiratory fluoroquinolone (as above) plus an intravenous anti-pneumococcal beta-lactam (as above).
2. For patients allergic to beta-lactam antibiotics, a fluoroquinolone *plus* aztreonam (2 g every 8 hours).
3. For patients at risk for *P aeruginosa*, add coverage for *P aeruginosa* and obtain cultures to confirm infection or to allow de-escalation of therapy: piperacillin-tazobactam, 3.375–4.5 g every 6 hours; cefepime, 1–2 g every 8 hours; imipenem, 0.5–1 g every 6 hours; meropenem, 1 g every 8 hours; or aztreonam 2 g every 8 hours.
4. For patients at risk for *Pseudomonas* infection AND who are critically ill, at increased risk for drug resistance, or if local incidence of monotherapy-resistant *Pseudomonas* is > 10%, consider adding either
   a. An anti-pseudomonal fluoroquinolone (ciprofloxacin 400 mg every 8–12 hours or levofloxacin 750 mg daily) *or*
   b. An aminoglycoside (gentamicin, tobramycin, amikacin, all weight-based dosing administered daily adjusted to appropriate trough levels).
5. For patients at risk for MRSA infection, add coverage for MRSA and obtain cultures and/or nasal PCR to confirm infection or to allow de-escalation of therapy: vancomycin, typically starting at 15 mg/kg intravenously every 12 hours with interval dosing based on kidney function to achieve serum trough concentration 15–20 mcg/mL or linezolid, 600 mg every 12 hours.

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*.
Recommendations assembled from Metlay JP et al; Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45–e67.

In outpatients with chronic heart, lung, liver, or kidney disease; diabetes mellitus; alcoholism; malignancy; or asplenia or who received antibiotic therapy within the past 90 days, the recommended treatment is a macrolide or doxycycline plus a beta-lactam (high-dose amoxicillin and amoxicillin-clavulanate are preferred to cefpodoxime and cefuroxime) or monotherapy with a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin).

The default duration of antibiotic therapy for CAP should be 5 days; factors that may affect therapy duration are clinical stability, etiology (MRSA and *P aeruginosa* require 7 days of therapy, for example), severity of illness, complications, and comorbid medical problems.

B. Treatment of Hospitalized and ICU Patients

1. Antibiotics—The most common etiologies of CAP in patients who require hospitalization but not intensive care are *S pneumoniae*, *M pneumoniae*, *C pneumoniae*, *H influenzae*, *Legionella* species, and respiratory viruses. Some patients have aspiration as an immediate precipitant to the CAP without a specific bacterial etiology. First-line therapy in hospitalized patients is the combination of a macrolide (clarithromycin or azithromycin) plus a beta-lactam (cefotaxime, ceftriaxone, ceftaroline, or ampicillin-sulbactam) or monotherapy with a respiratory fluoroquinolone (eg, moxifloxacin, gemifloxacin, or levofloxacin) (see Table 9–9).

Almost all patients admitted to a hospital for treatment of CAP receive intravenous antibiotics. However, no studies in hospitalized patients demonstrated superior outcomes with intravenous antibiotics compared with oral antibiotics, provided patients were able to tolerate oral therapy and the medication was well absorbed. Duration of inpatient antibiotic treatment is the same as for outpatients.

The most common etiologies of CAP in patients who require admission to intensive care are *S pneumoniae*, *Legionella* species, *H influenzae,* Enterobacteriaceae species, *S aureus*, *Pseudomonas* species, and respiratory viruses. First-line antibacterial therapy in ICU patients with CAP is an anti-pneumococcal beta-lactam (cefotaxime, ceftriaxone, ceftaroline, or ampicillin-sulbactam) *plus* either azithromycin or a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin).

Risk factors for *Pseudomonas*, Enterobacteriaceae, or MRSA infection must be considered when choosing empiric antibiotic therapy for inpatients with CAP. Specific risk factors for these organisms include (1) prior isolation of the pathogen, (2) inpatient hospitalization within the last 90 days, or (3) exposure to intravenous antibiotics within the last 90 days. In patients with specific risk factors for *Pseudomonas* infection, combine an anti-pneumococcal, anti-pseudomonal beta-lactam (piperacillin-tazobactam, cefepime, imipenem, meropenem) with either azithromycin or a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin). In critically ill patients, in those at increased risk for drug resistance, or if the unit incidence of monotherapy-resistant *Pseudomonas* is greater than 10%, consider use of two agents with anti-pseudomonal efficacy: either ciprofloxacin or levofloxacin plus the above anti-pneumococcal, anti-pseudomonal beta-lactam **or** an anti-pneumococcal, anti-pseudomonal beta-lactam plus an aminoglycoside (gentamicin, tobramycin, amikacin) plus either azithromycin or a respiratory fluoroquinolone. Patients with specific risk factors for MRSA should be treated with vancomycin or linezolid. Patients with very severe disease (respiratory failure requiring mechanical ventilation or septic shock) should also be strongly considered for MRSA therapy. Provided the patient is clinically improving, negative sputum and blood cultures obtained prior to initiation of antibiotics can support de-escalation of antibiotic therapy. Additionally, all patients prescribed vancomycin or linezolid should have swabs of the nasal passages for MRSA; if the swab results are negative, MRSA coverage can be safely de-escalated, even when adequate sputum samples have not been obtained.

Patients with CAP in whom influenza is detected should be treated with the antiviral oseltamavir, whether influenza is identified as a single pathogen or as a coinfection along with a bacterial pathogen. Oseltamavir treatment is most effective when begun within 2 days but may still be beneficial within several days after symptom onset, particularly in severe cases of CAP.

2. Adjunctive treatment—Conflicting data have emerged from RCTs regarding adjunctive treatment with corticosteroids in CAP. Meta-analyses of large studies have failed to find a mortality benefit in association with corticosteroid use in mild or moderate CAP, though there may be benefit in severe disease. Based on limited data and because of the potential for complications (eg, hyperglycemia), the 2019 Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines recommend against corticosteroids in the treatment CAP of any severity. Corticosteroid treatment of influenza pneumonia may be associated with higher mortality and should be avoided. Corticosteroid treatment is recommended for SARS-CoV-2 pneumonia when oxygen is required; see Chapter 32 for further discussion. Corticosteroids are recommended to be started or continued in patients with CAP who may also have severe septic shock, acute exacerbation of asthma or COPD, or adrenal insufficiency.

Prevention

Pneumococcal vaccines prevent or lessen the severity of pneumococcal infections in immunocompetent patients. Two pneumococcal vaccines for adults are available and approved for use in the United States: one containing capsular polysaccharide antigens of 23 common strains of *S pneumoniae* (Pneumovax 23) and a conjugate vaccine containing 13 common strains (Prevnar-13). Current recommendations are for sequential administration of the two vaccines in those aged 65 years or older and in immunocompromised persons, starting with Prevnar-13. Adults with chronic illness that increases the risk of CAP (see Chapter 30) should receive the 23-valent vaccine regardless of age. Immunocompromised patients and those at highest risk for fatal pneumococcal infections should receive a single revaccination of the 23-valent vaccine 5 years after the first vaccination regardless of age. Immunocompetent persons 65 years of age or older should receive a second dose of the 23-valent vaccine if the patient first received the vaccine 6 or more years previously and was under 65 years old at the time of first vaccination.

The seasonal influenza vaccine is effective in preventing severe disease due to influenza virus with a resulting positive impact on both primary influenza pneumonia and secondary bacterial pneumonias. The seasonal influenza vaccine is recommended annually for all persons older than 6 months without contraindications, with priority given to persons at risk for complications of influenza infection (persons aged 50 years or older, immunocompromised persons, residents of long-term care facilities, patients with pulmonary or cardiovascular disorders, pregnant women) as well as health care workers and others who may transmit influenza to high-risk patients.

Vaccinations against SARS-CoV-2 are recommended for all adults without contraindications. Vaccinations (including boosters) reduce the likelihood of infection, pneumonia, hospitalization, and mortality (see COVID-19 discussion, Chapter 32).

Hospitalized patients who would benefit from pneumococcal and influenza vaccines should be vaccinated during hospitalization. The two vaccines may be administered simultaneously as soon as the patient has stabilized.

When to Admit

Once a diagnosis of CAP is made, the first management decision is to determine the site of care: Is it safe to treat the patient at home or does he or she require hospital or intensive care admission? There are two widely used clinical prediction rules available to guide admission and triage decisions, the **Pneumonia Severity Index (PSI)** and the **CURB-65.**

A. Hospital Admission Decision

The PSI is a validated prediction model that uses 20 items from demographics, medical history, physical examination, laboratory results, and imaging to stratify patients into five risk groups. The PSI is weighted toward discrimination at low predicted mortality. In conjunction with clinical judgment, it facilitates safe decisions to treat CAP in the outpatient setting. An online PSI risk calculator is available at https://www.thecalculator.co/health/Pneumonia-Severity-Index-(PSI)-Calculator-977.html. The CURB-65 assesses five simple, independent predictors of increased mortality (**C**onfusion, **U**remia, **R**espiratory rate, **B**lood pressure, and age greater than **65**) to calculate a 30-day predicted mortality (https://www.mdcalc.com/curb-65-score-pneumonia-severity). Compared with the PSI, the simpler CURB-65 is less discriminating at low mortality but excellent at identifying patients with high mortality who may benefit from ICU-level care. A modified version (CRB-65) dispenses with BUN and eliminates the need for laboratory testing. Both have the advantage of simplicity: patients with zero CRB-65 predictors have a low predicted mortality (less than 1%) and usually do not need hospitalization; hospitalization should be considered for those with one or two predictors, since they have an increased risk of death; and urgent hospitalization (with consideration of ICU admission) is required for those with three or four predictors.

Hospital admission decision should also include circumstances of care independent of pneumonia severity, including comorbidities and the patient's ability to care for themselves effectively at home.

B. ICU Admission Decision

Expert opinion has defined major and minor criteria to identify patients at high risk for death. Major criteria are septic shock with need for vasopressor support and respiratory failure with need for mechanical ventilation. Minor criteria are respiratory rate = 30 breaths or more per minute, hypoxemia (defined as Pao_2/Fio_2 = 250 or less), hypothermia (core temperature less than 36.0°C), hypotension requiring aggressive fluid resuscitation, confusion/disorientation, multilobar pulmonary opacities, leukopenia due to infection with WBC less than 4000/mcL (less than 4.0×10^9/L), thrombocytopenia with platelet count less than 100,000/mcL (less than 100×10^9/L), uremia with BUN = 20 mg/dL or more (7.1 mmol/L or more), metabolic acidosis, or elevated serum lactate level. Either one major criterion or three or more minor criteria of illness severity generally require ICU-level care.

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2. Nosocomial Pneumonia (Hospital-Acquired & Ventilator-Associated)

ESSENTIALS OF DIAGNOSIS

- **Hospital-acquired pneumonia (HAP)** is diagnosed in patients with clinical features and imaging consistent with pneumonia, occurring > 48 hours after admission to the hospital and excluding any infections present at the time of admission.
- **Ventilator-associated pneumonia (VAP)** requires clinical features concerning for new pneumonia with positive respiratory samples developing > 48 hours following endotracheal intubation and mechanical ventilation.

General Considerations

Hospitalized patients carry different flora with different resistance patterns than healthy patients in the community, and their health status may place them at higher risk for more severe infection. The diagnostic approach and antibiotic treatment of patients with HAP is, therefore, different from patients with CAP. Similarly, management of patients in whom VAP develops following endotracheal intubation and mechanical ventilation should address issues specific to this group of patients.

Considered together, these nosocomial pneumonias (HAP or VAP) represent an important cause of morbidity and mortality despite widespread use of preventive measures, advances in diagnostic testing, and potent new antimicrobial agents. HAP is one of the most common causes of infection among hospital inpatients and carries the highest burden of morbidity and mortality. Patients in ICUs and those who are being mechanically ventilated are at the highest risk for HAP (and VAP) and experience higher morbidity and mortality from them than other inpatients. Definitive identification of the infectious cause of a lower respiratory infection is rarely available on presentation;

initial antibiotic treatment is therefore empiric and informed by epidemiologic and patient data rather than pathogen directed.

Definition & Pathogenesis

HAP develops more than 48 hours after admission to the hospital and VAP develops in a mechanically ventilated patient more than 48 hours after endotracheal intubation. Three factors distinguish nosocomial pneumonia from CAP: (1) different infectious causes; (2) different antibiotic susceptibility patterns, specifically, a higher incidence of drug resistance; and (3) poorer underlying health status of patients putting them at risk for more severe infections. Since access to the lower respiratory tract occurs primarily through microaspiration, nosocomial pneumonia starts with a change in upper respiratory tract flora. Colonization of the pharynx and possibly the stomach with bacteria is the most important step in the pathogenesis of nosocomial pneumonia. Pharyngeal colonization is promoted by exogenous factors (eg, instrumentation of the upper airway with nasogastric and endotracheal tubes; contact with personnel, equipment, and contaminated aerosols; treatment with broad-spectrum antibiotics that promote the emergence of drug-resistant organisms); and patient factors (eg, malnutrition, advanced age, altered consciousness, swallowing disorders, and underlying pulmonary and systemic diseases). Impaired cellular and mechanical defense mechanisms in the lungs of hospitalized patients raise the risk of infection after aspiration has occurred.

Gastric acid may play a role in protection against nosocomial pneumonias. Observational studies have suggested that elevation of gastric pH due to antacids, H_2-receptor antagonists, PPIs, or enteral feeding is associated with gastric microbial overgrowth, tracheobronchial colonization, and HAP/VAP. Moreover, a 2018 meta-analysis of randomized controlled trials suggested an increased risk of HAP among enterally fed patients receiving stress ulcer prophylaxis. The IDSA and other professional organizations recommend that acid-suppressive medications (H_2-receptor antagonists and PPIs) be given only to patients at high risk for stress gastritis.

The microbiology of the nosocomial pneumonias differs from CAP but is substantially the same among HAP and VAP. The most common organisms responsible for HAP and VAP include *S aureus* (both methicillin-sensitive *S aureus* and MRSA), *P aeruginosa*, gram-negative rods, including extended spectrum beta-lactamase (ESBL)–producing organisms (*Enterobacter* species, *K pneumoniae*, and *Escherichia coli*) and non-ESBL-producing organisms. VAP patients may be infected with *Acinetobacter* species and *S maltophilia*. Anaerobic organisms (*Bacteroides,* anaerobic streptococci, *Fusobacterium*) may also cause pneumonia in the hospitalized patient; when these organisms are isolated, they are commonly part of a polymicrobial flora. VAP occurring before hospital day 4 in a previous healthy person with no antibiotic exposure is more likely to involve oral flora with minimal resistance profiles than multidrug-resistant pathogens. However, multidrug-resistant pathogens may complicate early-onset VAP in patients with antibiotic exposure in preceding 90 days, recent hospitalization, or prior colonization with multidrug-resistant pathogens.

Clinical Findings

A. Symptoms and Signs

The symptoms and signs associated with nosocomial pneumonias are nonspecific. However, two or more clinical findings (fever, leukocytosis, purulent sputum, worsening respiratory status) along with one or more new or progressive pulmonary opacities on chest imaging are characteristic features of nosocomial pneumonia. Other findings include those listed above for CAP.

The differential diagnosis of new lower respiratory tract symptoms and signs in hospitalized patients includes heart failure, atelectasis, aspiration, ARDS, pulmonary thromboembolism, pulmonary hemorrhage, and medication reactions.

B. Laboratory Findings

Diagnostic evaluation for suspected nosocomial pneumonia includes blood cultures from two different sites. Blood cultures can identify the pathogen in 15–20% of patients with nosocomial pneumonias; positivity is associated with increased risk of complications and other sites of infection. Blood counts and clinical chemistry tests do not establish a specific diagnosis; however, they help define the severity of illness and identify complications. Serum procalcitonin levels are not sufficiently sensitive to rule out HAP or VAP but may allow discontinuation of antibiotic therapy. Thoracentesis for pleural fluid analysis should be considered in patients with pleural effusions.

Examination of lower respiratory tract secretions is attended by the same disadvantages as in CAP. Gram stains and cultures of sputum are neither sensitive nor specific in the diagnosis of nosocomial pneumonias; sensitivity of sputum results further decreases following antibiotic therapy, particularly after 72 hours of antibiotics. The identification of a bacterial organism by culture of lower respiratory tract secretions does not prove that the organism is a lower respiratory tract pathogen; however, it can be used to help identify bacterial antibiotic sensitivity patterns and as a guide to adjusting empiric therapy. Nasal swab for PCR detection of MRSA is recommended to guide de-escalation of broad-spectrum antibiotic therapy in patients with HAP and VAP.

C. Imaging

Radiographic findings in HAP/VAP are nonspecific and often confounded by other processes that led initially to hospitalization or ICU admission. (See CAP above.) Imaging may demonstrate complicating features including effusion, cavitation, or barotrauma.

D. Special Examinations

When HAP is suspected in a patient who subsequently requires mechanical ventilation, secretions may be obtained by spontaneous expectoration, sputum induction, nasotracheal suctioning, and endotracheal aspiration (qualitative

or semiquantitative samples), or more invasively via bronchoscopic sampling of the lower airways secretions (quantitative samples). The best approach remains a matter of debate, since qualitative or semiquantitative samples are more likely to return nonpathogenic organisms and are, thus, associated with higher antibiotic exposure (without improvement in mortality), while invasive quantitative sampling increases cost and patient risk. Invasive qualitative sampling is universally recommended when the patient does not improve during initial therapy directed at expected or isolated pathogens, or in immunocompromised persons in whom an opportunistic pathogen is suspected. Bronchoscopic sampling may also increase the diagnostic yield and identification of bacterial coinfection in patients intubated for SARS-CoV-2 pneumonia.

Treatment

The initial treatment of HAP and VAP is based on risk factors for MRSA and multiple drug-resistant pathogens (Table 9–10) as well as local antibiograms and mortality risk and is thus empiric (Table 9–11). The predictive capability of sets of risk factors for drug-resistant organisms in nosocomial pneumonia vary locally; strongest predictive factors include prior isolation of drug-resistant organisms, a high local prevalence of drug-resistant organisms, and antibiotic exposure within prior 90 days. Each hospital should generate antibiograms to guide the optimal choice of antibiotics with the goals of reducing exposure to unnecessary antibiotics and the development of antibiotic resistance, thus minimizing patient harm. Because of the high mortality rate, therapy should be started as soon as HAP or VAP is suspected. After results of cultures are available, it may be possible to narrow initially broad therapy to more specific agents. Endotracheal aspiration cultures have significant negative predictive value but limited positive predictive value in the diagnosis of specific infectious causes of HAP/VAP. If an invasive diagnostic approach to suspected VAP using quantitative culture of bronchoalveolar lavage (BAL), protected specimen brush (PSB), or blind bronchial sampling (BBS) is used, antibiotics can be withheld when results are below a diagnostic threshold (BAL less than 10^4 CFU/mL, PSB or BBS less than 10^3 CFU/mL). Duration of antibiotic therapy is 7 days, consistent with clinical response, but should be individualized based on the pathogen, severity of illness, response to therapy, and comorbid conditions.

For expanded discussions of specific antibiotics, see Chapter 30.

Table 9–10. Risk factors for multidrug-resistant (MDR) pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Pseudomonas* and other gram-negative bacilli in patients with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).

Risk factors for MDR pathogens
Antibiotic therapy in the preceding 90 days
Septic shock
Acute respiratory distress syndrome preceding VAP
≥ 5 days in hospital prior to occurrence of HAP/VAP
Acute renal replacement therapy prior to HAP/VAP onset
Treatment in a unit where > 10% of gram-negative isolates are resistant to an agent being considered for monotherapy
Treatment in a unit where local antibiotic susceptibility rates are not known
Risk factors for MRSA
Antibiotic therapy in the preceding 90 days
Renal replacement therapy in the preceding 30 days
Use of gastric acid suppressive agents
Positive culture or prior MRSA colonization, especially in the preceding 90 days
Hospitalization in a unit where > 20% of *S aureus* isolates are MRSA
Hospitalization in a unit where prevalence of MRSA is not known
Risk factors for *Pseudomonas aeruginosa* and other gram-negative bacilli
Antibiotic therapy in the preceding 90 days
Structural lung disease (COPD, especially with recurrent exacerbations; bronchiectasis; or cystic fibrosis)
Recent hospitalizations, especially with manipulation of the aerodigestive tract (nasoenteric nutrition, intubation)
High-quality Gram stain of respiratory secretions with numerous and predominant gram-negative bacilli
Positive culture for *P aeruginosa* in the past year

Data from Kalil AC et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63:e61.

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3. Anaerobic Pneumonia & Lung Abscess

ESSENTIALS OF DIAGNOSIS

- History of or predisposition to aspiration.
- Indolent symptoms, including fever, weight loss, and malaise.
- Poor dentition.
- Foul-smelling purulent sputum (in many patients).
- Infiltrate in dependent lung zone, with single or multiple areas of cavitation or pleural effusion.

Table 9–11. Recommended initial empiric antibiotics for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).

HAP not at high risk for mortality, or VAP with no risk factors for MRSA, MDR, or *Pseudomonas* and other gram-negative bacilli
USE **one** of the following:
Piperacillin-tazobactam, 4.5 g intravenously every 6 hours[1]
Cefepime, 2 g intravenously every 8 hours[1]
Levofloxacin, 750 mg intravenously daily
Imipenem, 500 mg intravenously every 6 hours[1]
Meropenem, 1 g intravenously every 8 hours[1]
HAP or VAP with risk factors for MRSA but no risk factors for MDR, *Pseudomonas*, and other gram-negative bacilli
USE **one** of the following:
Piperacillin-tazobactam, 4.5 g intravenously every 6 hours[1]
Cefepime, 2 g intravenously every 8 hours[1]
Ceftazidime, 2 g intravenously every 8 hours
Levofloxacin, 750 mg intravenously daily
Ciprofloxacin, 400 mg intravenously every 8 hours
Imipenem, 500 mg intravenously every 6 hours[1]
Meropenem, 1 g intravenously every 8 hours[1]
Aztreonam, 2 g intravenously every 8 hours
PLUS **one** of the following:
Vancomycin, 15 mg/kg intravenously every 8–12 hours with goal to target trough level = 15–20 mg/mL (consider a loading dose of 25–30 mg/kg once for severe illness)[2]
Linezolid, 600 mg intravenously every 12 hours
HAP with risk factors for *Pseudomonas* and other gram-negative bacilli, but no risk factors for MRSA and not at high risk for mortality
USE **one** of the following:
Piperacillin-tazobactam, 4.5 g intravenously every 6 hours[1]
Cefepime, 2 g intravenously every 8 hours[1]
Ceftazidime, 2 g intravenously every 8 hours
Imipenem, 500 mg intravenously every 6 hours[1]
Meropenem, 1 g intravenously every 8 hours[1]
Aztreonam, 2 g intravenously every 8 hours
PLUS **one** of the following:
Levofloxacin, 750 mg intravenously daily
Ciprofloxacin, 400 mg intravenously every 8 hours
Gentamicin, 5–7 mg/kg intravenously daily[2]
Tobramycin, 5–7 mg/kg intravenously daily[2]
Aztreonam, 2 g intravenously every 8 hours
HAP at high risk for mortality or VAP with risk factors for MRSA *and* risk factors for MDR, *Pseudomonas*, and other gram-negative bacilli
USE **one** of the following:
Piperacillin-tazobactam, 4.5 g intravenously every 6 hours[1]
Cefepime, 2 g intravenously every 8 hours[1]
Ceftazidime, 2 g intravenously every 8 hours
Imipenem, 500 mg intravenously every 6 hours[1]
Meropenem, 1 g intravenously every 8 hours[1]
Aztreonam, 2 g intravenously every 8 hours
PLUS **one** of the following:
Levofloxacin, 750 mg intravenously daily
Ciprofloxacin, 400 mg intravenously every 8 hours
Amikacin, 15–20 mg/kg intravenously daily[2]
Gentamicin, 5–7 mg/kg intravenously daily[2]
Tobramycin, 5–7 mg/kg intravenously daily[2]
Meropenem, 1 g intravenously every 8 hours[1]
Polymyxin B, 2.5–3.0 mg/kg per day divided in 2 daily intravenous doses
Colistin: consult clinical pharmacist for assistance with dosing
PLUS **one** of the following:
Vancomycin, 15 mg/kg intravenously every 8–12 hours with goal to target trough level = 15–20 mg/mL (consider a loading dose of 25–30 mg/kg once for severe illness)[2]
Linezolid, 600 mg intravenously every 12 hours

CrCl, creatinine clearance; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*.
[1]Extended infusions may be appropriate.
[2]Drug level monitoring and adjustment of dosing are required.
Data from Kalil AC et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63:e61.

General Considerations

Aspiration of small amounts of oropharyngeal secretions occurs during sleep in normal individuals but rarely causes disease. Sequelae of aspiration of larger amounts of material include nocturnal asthma, chemical pneumonitis, mechanical obstruction of airways by particulate matter, bronchiectasis, and pleuropulmonary infection. Individuals predisposed to disease induced by aspiration include those with depressed levels of consciousness due to drug or alcohol use, seizures, general anesthesia, or CNS disease; those with impaired deglutition due to esophageal disease or neurologic disorders; and those with tracheal or nasogastric tubes, which disrupt the mechanical defenses of the airways.

Periodontal disease and poor dental hygiene, which increase the number of anaerobic bacteria in aspirated material, are associated with a greater likelihood of anaerobic pleuropulmonary infection. Aspiration of infected oropharyngeal contents initially leads to pneumonia in dependent lung zones, such as the posterior segments of the upper lobes and superior and basilar segments of the lower lobes. Body position at the time of aspiration determines which lung zones are dependent. The onset of symptoms is insidious. By the time the patient seeks medical attention, necrotizing pneumonia, lung abscess, or empyema may be apparent.

In most cases of aspiration and necrotizing pneumonia, lung abscess, and empyema, multiple species of anaerobic bacteria are causing the infection. Most of the remaining cases are caused by infection with both anaerobic and aerobic bacteria. *Prevotella melaninogenica*, *Peptostreptococcus*, *Fusobacterium nucleatum*, and *Bacteroides* species are commonly isolated anaerobic bacteria.

Clinical Findings

A. Symptoms and Signs

Patients with anaerobic pleuropulmonary infection usually present with constitutional symptoms, such as fever, weight loss, and malaise. Cough with expectoration of foul-smelling purulent sputum suggests anaerobic infection, though the absence of productive cough does not rule out such an infection. Dentition is often poor. Patients are rarely edentulous; if so, an obstructing bronchial lesion may be present.

B. Laboratory Findings

Expectorated sputum cultures may be difficult to interpret due to contaminating upper respiratory tract flora, but high colony count of a particular microorganism on Gram stain or in culture likely represents a true pathogen. Anaerobes and facultative anaerobes are difficult to recover on any culture, particularly following initiation of antibiotics; pleural fluid from empyema may be revealing.

C. Imaging

The different types of anaerobic pleuropulmonary infection are distinguished by their radiographic appearance. **Lung abscess** appears as a thick-walled solitary cavity surrounded by consolidation. An air-fluid level is usually present. Other causes of cavitary lung disease (tuberculosis, mycosis, cancer, infarction, necrobiotic nodules in rheumatoid arthritis, and pulmonary vasculitides) should be excluded. **Necrotizing pneumonia** is distinguished by multiple areas of cavitation within an area of consolidation. **Empyema** is characterized by the presence of purulent pleural fluid and may accompany either of the other two radiographic findings. Ultrasonography is of value in locating fluid and may also reveal pleural loculations.

Treatment

Medications of choice are directed at anaerobic organisms or facultative anaerobic streptococci and include a beta-lactam/lactamase inhibitor combination, carbapenem, or clindamycin. Second-line therapy includes a combination of penicillin and metronidazole. Duration of antibiotic therapy for anaerobic pneumonia is controversial, but it is usually given for a minimum of 3 weeks, with some experts recommending treatment until the abscess cavity has resolved on imaging.

Peripheral lung abscess must be carefully distinguished from empyema because empyema requires tube thoracostomy; if tube thoracostomy is placed inadvertently into an abscess cavity, complications, such as a bronchopleural fistula, may result. Thoracic surgery consultation is recommended for large or nonresolving abscesses or for abscesses that rupture into the pleural space. Rarely, a large abscess requires surgical intervention (percutaneous drainage, segmentectomy, lobectomy, or pneumonectomy).

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PULMONARY INFILTRATES IN IMMUNOCOMPROMISED PATIENTS

Pulmonary infiltrates in immunocompromised patients (patients with HIV disease, absolute neutrophil counts less than 1000/mcL [less than 1.0×10^9/L], current or recent exposure to myelosuppressive or immunosuppressive medications, or those taking more than 20 mg/day of prednisone or equivalent for more than 4 weeks) may arise from infectious or noninfectious causes. Infection may be due to bacterial, mycobacterial, fungal, protozoal, helminthic, or viral pathogens. Noninfectious processes, such as pulmonary edema, alveolar hemorrhage, medication reactions, pulmonary thromboembolic disease, malignancy, and radiation pneumonitis, may mimic infection.

Although almost any pathogen can cause pneumonia in an immunocompromised patient, two clinical tools help the clinician narrow the differential diagnosis. The first is knowledge of the underlying immunologic defect. Specific immunologic defects are associated with particular infections. Defects in humoral immunity predispose to bacterial infections; defects in cellular immunity lead to infections with viruses, fungi, mycobacteria, and protozoa. Neutropenia and impaired granulocyte function predispose to

infections from *S aureus*, *Aspergillus*, gram-negative bacilli, and *Candida*. Second, the time course of infection also provides clues to the etiology of pneumonia in immunocompromised patients. A fulminant pneumonia is often caused by bacterial infection, whereas an insidious pneumonia is more apt to be caused by viral, fungal, protozoal, or mycobacterial infection. Pneumonia occurring within 2–4 weeks after organ transplantation is usually bacterial, whereas several months or more after transplantation, *P jirovecii*, viruses (eg, cytomegalovirus) and fungi (eg, *Aspergillus*) are encountered more often.

Clinical Findings

Chest radiography is rarely helpful in narrowing the differential diagnosis. Examination of expectorated sputum for bacteria, fungi, mycobacteria, *Legionella*, and *P jirovecii* is important and may preclude the need for expensive, invasive diagnostic procedures. Sputum induction is often necessary for diagnosis. The sensitivity of induced sputum for detection of *P jirovecii* depends on institutional expertise, number of specimens analyzed, and detection methods.

Routine evaluation frequently fails to identify a causative organism. The clinician may begin empiric antimicrobial therapy before proceeding to invasive procedures, such as bronchoscopy, transthoracic needle aspiration, or open lung biopsy. The approach to management must be based on the severity of the pulmonary infection, the underlying disease, the risks of empiric therapy, and local expertise and experience with diagnostic procedures. BAL using flexible bronchoscopy is a safe and effective method for obtaining representative pulmonary secretions for microbiologic studies. It involves less risk of bleeding and other complications than transbronchial biopsy. BAL is especially suitable for the diagnosis of *P jirovecii* pneumonia in patients with HIV/AIDS when induced sputum analysis is negative. Surgical lung biopsy, now often performed by video-assisted thoracoscopy, provides the definitive option for diagnosis of pulmonary infiltrates in immunocompromised patients; however, a specific diagnosis is obtained in only about two-thirds of cases, and the information obtained may not affect the outcome.

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PULMONARY TUBERCULOSIS

ESSENTIALS OF DIAGNOSIS

- Fatigue, weight loss, fever, night sweats, and productive cough.
- Risk factors for acquisition of infection: household exposure, incarceration, drug use, travel to or residence in endemic area.
- Chest radiograph: pulmonary opacities, including nodular or cavitating.
- Acid-fast bacilli on smear of sputum, rapid molecular testing positive, or sputum culture positive for *M tuberculosis*.

General Considerations

Tuberculosis is one of the world's most widespread and deadly illnesses. *M tuberculosis*, the organism that causes tuberculosis infection and disease, infects one-quarter of the world's population, nearly 2 billion people. Based on WHO data, there were 10 million new cases of tuberculosis worldwide in 2020 with 1.5 million people dying of the disease, a provisional increase in mortality for the first time since 2005, with a global increase in case-fatality rate to 15%. Reporting data suggest considerable disruption to tuberculosis diagnosis and treatment due to the COVID-19 pandemic. While most incident cases occur in low- and middle-income countries, tuberculosis is present in all regions of the world. In the United States, per the CDC, an estimated 13 million people are infected with *M tuberculosis*, and in 2020, there were 7174 reported active cases. Tuberculosis occurs disproportionately among disadvantaged populations, such as the malnourished, homeless, and those living in overcrowded and substandard housing. There is an increased occurrence of tuberculosis among HIV-positive individuals.

Infection with *M tuberculosis* begins when a susceptible person inhales airborne droplet nuclei containing viable organisms. Tubercle bacilli that reach the alveoli are ingested by alveolar macrophages. Infection follows if the inoculum escapes alveolar macrophage microbicidal activity. Once infection is established, lymphatic and hematogenous dissemination of tuberculosis typically occurs before the development of an effective immune response. This stage of infection, **primary tuberculosis,** is usually clinically and radiographically silent. In most persons with intact cell-mediated immunity, T-cells and macrophages surround the organisms in granulomas that limit their multiplication and spread. The infection is contained but not eradicated, since viable organisms may lie dormant within granulomas for years to decades.

Individuals with **latent tuberculosis infection** do not have active disease and cannot transmit the organism to others. However, reactivation of disease may occur if the patient's immune defenses are impaired. **Active tuberculosis** will develop in 5–15% of individuals with latent tuberculosis infection who are not given preventive therapy; half of

these cases occur in the 2 years following primary infection. Diverse conditions such as gastrectomy, silicosis, diabetes mellitus, and an impaired immune response (eg, HIV infection; therapy with corticosteroids, tumor necrosis factor inhibitors or other immunosuppressive drugs) are associated with an increased risk of reactivation.

In approximately 5% of cases, the immune response is inadequate to contain the primary infection and **progressive primary tuberculosis** develops, accompanied by both pulmonary and constitutional symptoms. The clinical presentation does not definitively distinguish primary disease from reactivation of latent tuberculosis infection. Standard teaching has held that 90% of tuberculosis in adults represents activation of latent disease. However, DNA fingerprinting of the bacillus suggests that as many as one-third of new cases of tuberculosis in urban populations are primary infections resulting from person-to-person transmission.

The prevalence of drug-resistant strains is increasing worldwide, though in resourced countries including the United States, the rate of multidrug-resistant isolates has fallen to less than 1%. Risk factors for drug resistance include immigration from countries with a high prevalence of drug-resistant tuberculosis, close and prolonged contact with individuals with drug-resistant tuberculosis, unsuccessful previous therapy, and nonadherence to treatment. Drug resistance may be single or multiple. **Drug-resistant tuberculosis** is resistant to one first-line antituberculous drug, either isoniazid or rifampin. **Multidrug-resistant tuberculosis** is resistant to isoniazid and rifampin, and possibly additional agents. **Extensively drug-resistant tuberculosis** is resistant to isoniazid, rifampin, fluoroquinolones, and either aminoglycosides or capreomycin or both. Outcomes of drug-resistant tuberculosis treatment are worse than when the isolate is drug-sensitive, and outcomes appear to vary with HIV status. In a review of extensively drug-resistant tuberculosis cases in the United States, mortality was 10% in HIV-negative patients and 68% in HIV-positive patients.

Clinical Findings

A. Symptoms and Signs

The patient with pulmonary tuberculosis typically presents with slowly progressive constitutional symptoms of malaise, anorexia, weight loss, fever, and night sweats. Chronic cough is the most common pulmonary symptom. It may be dry at first but typically becomes productive of purulent sputum as the disease progresses. Blood-streaked sputum is common, but significant hemoptysis is rarely a presenting symptom; life-threatening hemoptysis may occur in advanced disease. Dyspnea is unusual unless there is extensive disease. On physical examination, the patient appears chronically ill and malnourished. On chest examination, there are no physical findings specific for tuberculosis infection. The examination may be normal or may reveal classic findings such as posttussive apical rales.

B. Laboratory Findings

Definitive diagnosis depends on recovery of *M tuberculosis* from cultures or identification of the organism by DNA or RNA amplification techniques (in concert with appropriate clinical context). At least three consecutive morning sputum specimens are advised, and samples should be collected 8 hours apart. Acid-fast staining of a sputum smear is performed initially as a screening method, with sensitivity and negative predictive values that are low (50–80%) with a single smear but may improve to 90% with serial sampling. Smear sensitivity is lower in HIV-coinfected patients. Demonstration of acid-fast bacilli on sputum smear does not establish a diagnosis of *M tuberculosis* since nontuberculous mycobacteria may colonize the airways and are increasingly recognized to cause clinical illness in patients with underlying structural lung disease.

In patients thought to have tuberculosis who cannot produce satisfactory specimens or when the smear of the spontaneously expectorated sputum is negative for acid-fast bacilli, sputum induction with 3% hypertonic saline should be performed. Flexible bronchoscopy with bronchial washings has similar diagnostic yield to induced sputum; transbronchial lung biopsies do not significantly increase the diagnostic yield but may lead to earlier diagnosis by identifying tissue granulomas. Post-bronchoscopy expectorated sputum specimens should be collected. Positive blood cultures for *M tuberculosis* are uncommon in patients with normal CD4 cell counts, but the organism may be cultured from blood in up to 50% of HIV-seropositive patients with tuberculosis whose CD4 cell counts are less than 100/mcL (less than 0.1×10^9/L); mycobacterial blood cultures should be obtained in such patients.

The slow rate of mycobacterial growth; the urgency to provide early, appropriate treatment to patients to improve their outcomes and limit community spread; and concerns about potential drug toxicities in patients treated empirically who do not have tuberculosis infection have fostered the use of rapid diagnostic techniques (Table 9–12). Molecular diagnostics offer multiple options and many advantages, though at increased expense. Nucleic acid amplification testing not only detects *M tuberculosis* (NAAT-TB) but also identifies resistance markers (NAAT-R). NAAT-TB can identify *M tuberculosis* within hours of sputum processing, allowing early isolation and treatment, though the negative predictive value is lower in smear-negative patients. NAAT-R allows rapid identification of primary drug resistance and has previously been indicated in the following patients: (1) those treated previously for tuberculosis, (2) those born (or who lived for more than 1 year) in a country with moderate tuberculosis incidence or a high incidence of multiple drug-resistant isolates, (3) contacts of patients with multidrug-resistant tuberculosis, or (4) those who are HIV seropositive. In view of the rapidity of result in concert with rifampin resistance identification, the WHO issued continued guidance in 2020 that rapid molecular testing is the ideal initial test for diagnosis and resistance profiling in persons in whom pulmonary or extrapulmonary tuberculosis is suspected.

Needle biopsy of the pleura reveals granulomatous inflammation in approximately 60% of patients with pleural effusions caused by *M tuberculosis*. Pleural fluid cultures are positive for *M tuberculosis* in 23–58% of cases of pleural tuberculosis. Culture of three pleural biopsy

Table 9–12. Essential laboratory tests for the detection of *Mycobacterium tuberculosis*.[1]

Test	Time to Result	Test Characteristics
Acid-fast bacilli light microscopy	1 day	Three morning specimens recommended. Combined sensitivity of 70% (54% for the first specimen, 11% for the second specimen, and 5% for the third specimen). First morning specimen increased yield by 12% compared to spot specimen.
Nucleic acid amplification test, detection (NAAT-TB)	1 day	Sensitivity/specificity high for smear-positive specimens, 85–97% for both; sensitivity falls in smear-negative specimens to ~66%. A positive NAAT in smear-negative patients with intermediate to high (> 30%) pretest probability of *M tuberculosis* infection is helpful while a negative NAAT is not. Should not be ordered in patients with low pretest probability of *M tuberculosis* infection.
Nucleic acid amplification test, resistance markers (NAAT-R)	1–2 days	Multiple assays for rifampin and isoniazid are available. Specificity uniformly high, > 98%. Sensitivity varies from about 84% to 96%, increases with multiple specimens. See text for indications for testing.
Mycobacterial growth detection Liquid (broth based) medium Solid (agar or egg based) medium	Up to 6–8 weeks Avg 10–14 days Avg 3–4 weeks	Liquid culture methods are more sensitive than solid culture methods (~90% and 76%, respectively) with shorter time to detection but higher contamination with bacterial growth. Specificity exceeds 99% for all methods.
Identification of *M tuberculosis* complex by DNA probe or high-performance liquid chromatography	1 day[1]	May be useful in areas of low *M tuberculosis* incidence where nontuberculous mycobacteria are commonly isolated.
First-line drug susceptibility testing (liquid medium)	1–2 weeks[1]	Gold standard. Should be performed routinely on the initial isolate.
Second-line and novel compound drug susceptibility testing Liquid (broth based) medium Solid (agar or egg based) medium	 1–2 weeks[1] 3–4 weeks[1]	

[1]Following detection of mycobacterial growth.
Adapted from Diagnostic Standards and Classification of Tuberculosis in Adults and Children. This official statement of the American Thoracic Society and the Centers for Disease Control and Prevention was adopted by the ATS Board of Directors, July 1999. This statement was endorsed by the Council of the Infectious Disease Society of America, September 1999. Am J Respir Crit Care Med. 2000;161:1376.

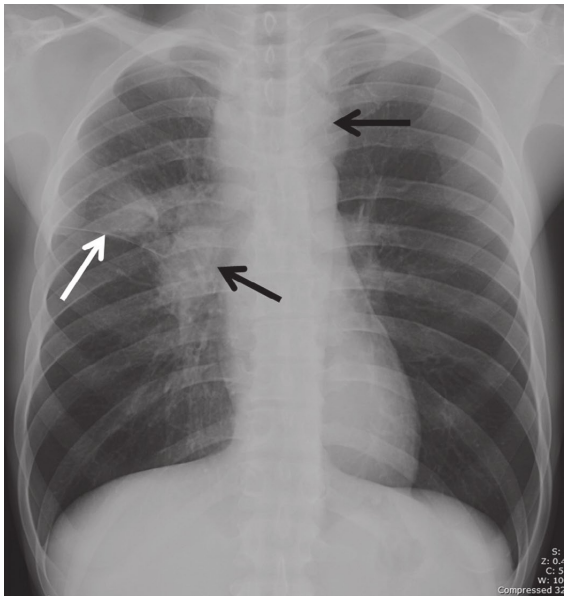
specimens combined with microscopic examination of a pleural biopsy yields a diagnosis in up to 90% of patients with pleural tuberculosis. Tests for pleural fluid adenosine deaminase (approximately 90% sensitivity and specificity for pleural tuberculosis at levels greater than 70 U/L) and interferon-gamma (89% sensitivity, 97% specificity in a recent meta-analysis) can be extremely helpful diagnostic aids, particularly in making decisions to pursue invasive testing in complex cases.

C. Imaging

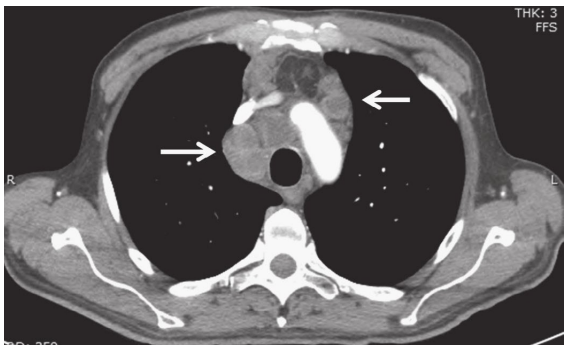
Contrary to traditional teaching, molecular analysis demonstrates that radiographic abnormalities in pulmonary tuberculosis do not distinguish primary disease from reactivation of latent tuberculosis (Figure 9–4). The only independent predictor of an atypical pattern on chest radiograph—that is, not associated with upper lobe or cavitary disease—is an impaired patient immune response. The chest imaging pattern traditionally associated with primary disease includes small unilateral infiltrates, hilar and paratracheal lymph node enlargement, and segmental atelectasis. Pleural effusion is present in 30–40% of patients, sometimes as the sole radiographic abnormality. Reactivation tuberculosis traditionally has been associated with fibrocavitary apical disease, discrete nodules, and pneumonic infiltrates, usually in the apical or posterior segments of the upper lobes or in the superior segments of the lower lobes. Radiographic evidence of disease in other locations may be present in up to 30% of patients.

In elderly patients, lower lobe infiltrates with or without pleural effusion are frequently encountered. A "miliary" pattern (diffuse small nodular densities) can be seen with hematologic or lymphatic dissemination of the organism. Immunocompromised patients—particularly those with late-stage HIV infection—often display lower lung zone, diffuse, or miliary infiltrates; pleural effusions; and involvement of hilar and, in particular, mediastinal lymph nodes.

Resolution of active tuberculosis leaves characteristic radiographic findings. Dense nodules in the pulmonary hila, with or without obvious calcification, upper lobe fibronodular scarring, and bronchiectasis with volume loss are common findings. Ghon (calcified primary focus) and Ranke (calcified primary focus and calcified hilar lymph node) complexes are seen in a minority of patients.



A



B

▲ **Figure 9–4.** Pulmonary tuberculosis. Primary pulmonary tuberculosis in a 20-year-old man with chest radiograph **(A)** showing right upper lobe consolidation (white arrow) and right hilar and mediastinal lymphadenopathy (black arrows) and contrast-enhanced CT scan **(B)** showing mediastinal lymphadenopathy (arrows). (Used, with permission, from Carlos Santiago Restrepo, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

D. Special Examinations

Testing for latent tuberculosis infection is used to evaluate an asymptomatic person in whom *M tuberculosis* infection is suspected (eg, following contact exposure) or to establish the prevalence of tuberculosis infection in a population. Testing may be used in a person with symptoms of active tuberculosis, but a positive test does not distinguish between active and latent infection, and a negative test does not rule out active disease. Routine testing of individuals at low risk for tuberculosis is not recommended. Empiric treatment of latent tuberculosis without testing is considered appropriate in HIV-infected persons or in young (less than 5 years old) household contacts of persons with active tuberculosis in endemic areas.

The traditional approach to testing for latent tuberculosis infection is the **tuberculin skin test.** The Mantoux test is the preferred method: 0.1 mL of purified protein derivative (PPD) containing 5 tuberculin units is injected intradermally on the volar surface of the forearm using a 27-gauge needle on a tuberculin syringe. The **transverse width in millimeters of induration** at the skin test site is measured after 48–72 hours. To optimize test performance, criteria for determining a positive reaction vary depending on the likelihood of infection. Table 9–13 summarizes the criteria established by the CDC for interpretation of the Mantoux tuberculin skin test. Sensitivity and specificity of the tuberculin skin test are high: 77% and 97%, respectively. Specificity falls to 59% in populations previously vaccinated with bacillus Calmette-Guérin (BCG, an attenuated form of *Mycobacterium bovis*). False-negative tuberculin skin test reactions may result from improper testing technique; concurrent infections, including fulminant tuberculosis; malnutrition; advanced age; immunologic disorders; malignancy; corticosteroid therapy; CKD; and HIV infection. Some individuals with latent tuberculosis infection may have a negative tuberculin skin test when tested many years after exposure. Anergy testing is not recommended for routine use to distinguish a true-negative result from anergy. Poor anergy test standardization and lack of outcome data limit the evaluation of its effectiveness. Interpretation of the tuberculin skin test in persons who have previously received BCG vaccination is the same as in those who have not had BCG.

Interferon gamma release assays (including the QuantiFERON and T-SPOT tests) are in vitro assays of CD4+ T-cell–mediated interferon gamma release in response to stimulation by specific *M tuberculosis* antigens. The antigens are absent from all BCG strains and most nontuberculous mycobacteria; therefore, in whole blood, the specificity of interferon gamma release assays is superior to the tuberculin skin test in BCG-vaccinated individuals. Sensitivity is comparable to the tuberculin skin test: 60–90% depending on the specific assay and study population. Sensitivity is reduced by HIV infection, particularly in patients with low CD4 counts. Specificity is high, greater than 95%. Potential advantages of interferon gamma release assay testing include fewer false-positive results from prior BCG vaccination, better discrimination of positive responses due to nontuberculous mycobacteria, and the requirement for only one patient contact (ie, no need for the patient to return to have the tuberculin skin test read 48–72 hours later). Disadvantages include the need for specialized laboratory equipment and personnel and the substantially increased cost compared to the tuberculin skin test.

In endemic areas, interferon gamma release assays are no more sensitive than the tuberculin skin test in active tuberculosis (20–40% false-negative rate) and cannot distinguish active from latent disease. Interferon gamma release assays should not be used to exclude active tuberculosis.

Table 9–13. Classification of positive tuberculin skin test reactions.[1]

Induration Size	Group
≥ 5 mm	1. HIV-positive persons. 2. Recent contacts of a person with infectious tuberculosis. 3. Persons with fibrotic changes on chest radiographs suggestive of prior tuberculosis. 4. Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of > 15 mg/day of prednisone for 1 month or more, or those taking TNF-alpha antagonists).
≥ 10 mm	1. Recent immigrants (< 5 years) from countries with a high prevalence of tuberculosis (eg, Asia, Africa, Latin America). 2. HIV-negative injection drug users. 3. Mycobacteriology laboratory personnel. 4. Residents of and employees in high-risk congregate settings: correctional institutions; long-term care facilities; hospitals and other health care facilities; residential facilities for HIV/AIDS patients; and homeless shelters. 5. Persons with medical conditions that increase the risk of progression to tuberculosis disease: gastrectomy, weight loss to ≥ 10% below ideal body weight, jejunoileal bypass, diabetes mellitus, silicosis, advanced CKD, some hematologic disorders (eg, leukemias, lymphomas), and other specific malignancies (eg, carcinoma of the head or neck and lung). 6. Children younger than 4 years or infants, children, and adolescents exposed to adults at high risk.
≥ 15 mm	1. Persons with no known risk factors for tuberculosis.

[1]A tuberculin skin test reaction is considered positive if the transverse diameter of the *indurated* area reaches the size required for the specific group. All other reactions are considered negative.
Data from https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm.

Guidelines established by the CDC allow interferon gamma release assays to be used interchangeably with the tuberculin skin testing in the diagnosis of latent tuberculosis infection. Interferon gamma release assays are preferred in patients with prior BCG vaccination; the tuberculin skin test is preferred in children under 5 years old. Routine use of both tests is not recommended. In individuals with a positive tuberculin skin test but a low prior probability of latent tuberculosis infection and low-risk for progression to active disease, the interferon gamma release assay may be helpful as a confirmatory test to exclude a false-positive tuberculin skin test.

Treatment

A. General Measures

The goals of therapy are to cure the individual patient, minimize risk of morbidity and mortality related to treatment, reduce transmission of *M tuberculosis* to other persons, and prevent the emergence of clinically significant drug resistance in tubercle bacilli. The basic principles of antituberculous treatment are (1) to administer multiple medications to which the organisms are susceptible; (2) to provide the safest, most effective therapy for the shortest period of time; (3) to ensure adherence to therapy; and (4) to add at least two new antituberculous agents to a regimen when treatment failure is suspected.

All suspected and confirmed cases of tuberculosis should be reported promptly to local and state public health authorities. Patients with tuberculosis should be treated by clinicians who are skilled in the management of this infection. Clinical expertise is especially important in cases of drug-resistant tuberculosis.

Nonadherence to antituberculous treatment is a major cause of treatment failure, continued transmission of tuberculosis, and development of medication resistance. Adherence to treatment can be improved by providing detailed patient education about tuberculosis and its treatment in addition to a case manager who oversees all aspects of an individual patient's care. **Directly observed therapy (DOT),** which requires that a health care worker physically observe the patient ingest antituberculous medications in the home, clinic, hospital, or elsewhere, also improves adherence to treatment. The importance of direct observation of therapy cannot be overemphasized. The CDC recommends DOT for all patients with drug-resistant tuberculosis and for those receiving intermittent (twice- or thrice-weekly) therapy. Electronic DOT ("eDOT") is promising as a more efficient care model in selected populations.

Hospitalization for initial therapy of tuberculosis is not necessary for most patients. It should be considered if a patient is incapable of self-care or is likely to expose new, susceptible individuals to tuberculosis. Hospitalized patients with active disease require a private room with appropriate environmental controls, including negative-pressure ventilation where available, until tubercle bacilli are no longer found in their sputum ("smear-negative") on three consecutive smears taken on separate days.

Characteristics of antituberculous drugs are provided in Table 9–14. Additional treatment considerations can be found in Chapter 33. More complete information can be obtained from the CDC's Division of Tuberculosis Elimination website at https://www.cdc.gov/tb/topic/treatment/default.htm or the WHO tuberculosis website at https://www.who.int/health-topics/tuberculosis/.

B. Treatment of Tuberculosis in HIV-Negative Persons

Most patients with previously untreated pulmonary tuberculosis can be effectively treated with either a 6-month or a

Table 9–14. Characteristics of antituberculous medications.

Medication	Most Common Side Effects	Tests for Side Effects	Drug Interactions	Remarks
Isoniazid	Peripheral neuropathy, hepatitis, rash, mild CNS effects.	AST and ALT; neurologic examination.	Phenytoin (synergistic); disulfiram.	Bactericidal to both extracellular and intracellular organisms. Pyridoxine, 25–50 mg orally daily, is given as prophylaxis for neuropathy; 50–100 mg orally daily as treatment for it.
Rifampin	Hepatitis, fever, rash, flu-like illness, GI upset, bleeding problems, kidney failure.	CBC, platelets, AST and ALT.	Rifampin inhibits the effect of oral contraceptives, quinidine, corticosteroids, warfarin, methadone, digoxin, oral hypoglycemics; aminosalicylic acid may interfere with absorption of rifampin. Significant interactions with protease inhibitors and nonnucleoside reverse transcriptase inhibitors.	Bactericidal to all populations of organisms. Colors urine and other body secretions orange. May discolor contact lenses.
Rifapentine	Bone marrow suppression, hematuria/pyuria, hepatitis, GI upset, flu-like illness.	CBC, platelets, AST and ALT.	Strong cytochrome P450 inducer with multiple drug interactions. Use in HIV patients receiving antiretroviral therapy should be limited to experts in antiretroviral therapy.	Bactericidal to both extracellular and intracellular organisms. Colors urine and other body secretions orange. Long half-life, can be administered weekly in LTBI prophylaxis. Not for use in induction phase of therapy.
Pyrazinamide	Hyperuricemia, hepatotoxicity, rash, GI upset, joint aches.	Uric acid, AST, ALT.	Rare.	Bactericidal to intracellular organisms.
Ethambutol	Optic neuritis (reversible with discontinuance of drug; rare at 15 mg/kg); rash.	Red-green color discrimination and visual acuity.	Rare.	Bacteriostatic to both intracellular and extracellular organisms. Mainly used to inhibit development of resistant mutants. Use with caution in kidney disease or when ophthalmologic testing is not feasible.
Streptomycin	Eighth nerve damage, nephrotoxicity.	Vestibular function (audiograms); BUN and creatinine.	Neuromuscular blocking agents may be potentiated and cause prolonged paralysis.	Bactericidal to extracellular organisms. Use with caution in older patients or those with kidney disease.

LTBI, latent tuberculosis infection.

9-month regimen, though the 6-month regimen is preferred. The initial phase of a 6-month regimen consists of 2 months of daily isoniazid, rifampin, pyrazinamide, and ethambutol. Once the isolate is determined to be isoniazid-sensitive, ethambutol may be discontinued. If the *M tuberculosis* isolate is susceptible to isoniazid and rifampin, the second phase of therapy consists of isoniazid and rifampin for a minimum of 4 additional months, with treatment to extend at least 3 months beyond documentation of conversion of sputum cultures to negative for *M tuberculosis*. If DOT is used, medications may be given intermittently using one of three regimens: (1) Daily isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin two or three times each week for 4 months if susceptibility to isoniazid and rifampin is demonstrated. (2) Daily isoniazid, rifampin, pyrazinamide, and ethambutol for 2 weeks, then administration of the same agents twice a week for 6 weeks followed by administration of isoniazid and rifampin twice each week for 4 months if susceptibility to isoniazid and rifampin is demonstrated. (3) Isoniazid, rifampin, pyrazinamide, and ethambutol three times a week for 6 months.

Patients who cannot or should not (eg, pregnant women) take pyrazinamide should receive daily isoniazid and rifampin along with ethambutol for 4–8 weeks. If susceptibility to isoniazid and rifampin is demonstrated or drug resistance is unlikely, ethambutol can be discontinued, and isoniazid and rifampin may be given for a total of 9 months of therapy. If drug resistance is a concern, patients should receive isoniazid, rifampin, and ethambutol for 9 months. Patients with smear- and culture-negative disease (eg, pulmonary tuberculosis diagnosed on clinical grounds) and patients for whom drug susceptibility testing is not available can be treated with 6 months of

Table 9–15. Recommended dosages for the initial treatment of tuberculosis.[1]

Medication	Daily[2]	Cost[3]/Day	Twice a Week[2]	Cost[3]/Wk	Three Times a Week[2]	Cost[3]/Wk
Isoniazid	5 mg/kg Max: 300 mg/dose	$0.31/300 mg	15 mg/kg Max: 900 mg/dose	$1.86	15 mg/kg Max: 900 mg/dose	$2.79
Rifampin	10 mg/kg Max: 600 mg/dose	$2.66/600 mg	10 mg/kg Max: 600 mg/dose	$5.32	10 mg/kg Max: 600 mg/dose	$7.98
Pyrazinamide	18.2–26.3 mg/kg Max: 2 g/dose	$24.33/2 g	Weight-based dosing: see references below[1]	—	Weight-based dosing: see references below[1]	—
Ethambutol	14.5–21.1 mg/kg Max: 1.6 g/dose	$3.74/1.6 g	Weight-based dosing: see references below[1]	—	Weight-based dosing: see references below[1]	—

[1]Data from Nahid P et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63:e147.
[2]All dosing regimens should be used with directly observed therapy.
[3]IBM Micromedex Red Book (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www-micromedexsolutions-com.proxy.hsl.ucdenver.edu/, accessed March 15, 2022.

isoniazid and rifampin combined with pyrazinamide for the first 2 months. This regimen assumes low prevalence of drug resistance. Previous guidelines have used streptomycin interchangeably with ethambutol. Increasing worldwide streptomycin resistance has made this medication less useful as empiric therapy.

When a twice-weekly or thrice-weekly regimen is used instead of a daily regimen, the dosages of isoniazid, pyrazinamide, and ethambutol or streptomycin must be increased. Recommended dosages for the initial treatment of tuberculosis are listed in Table 9–15. Fixed-dose combinations of isoniazid and rifampin (Rifamate) and of isoniazid, rifampin, and pyrazinamide (Rifater) are available to simplify treatment. Single tablets improve compliance but are more expensive than the individual medications purchased separately.

C. Treatment of Tuberculosis in HIV-Positive Persons

Management of tuberculosis is complex in patients with concomitant HIV disease. Experts in the management of both tuberculosis and HIV disease should be involved in the care of such patients. The CDC has published detailed recommendations for the treatment of tuberculosis in HIV-positive patients (https://www.cdc.gov/tb/topic/treatment/tbhiv.htm).

The basic approach to HIV-positive patients with tuberculosis is similar to that detailed above for patients without HIV disease. Additional considerations in HIV-positive patients include (1) longer duration of therapy and (2) drug interactions between rifamycin derivatives such as rifampin and rifabutin used to treat tuberculosis and some of the protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs) used to treat HIV. DOT is recommended for all HIV-positive tuberculosis patients. Pyridoxine (vitamin B_6), 25–50 mg orally each day, should be administered to all HIV-positive patients being treated with isoniazid to reduce central and peripheral nervous system side effects.

D. Treatment of Drug-Resistant Tuberculosis

Patients with drug-resistant *M tuberculosis* infection require careful supervision and management. Clinicians who are unfamiliar with the treatment of drug-resistant tuberculosis should seek expert advice. Tuberculosis resistant only to isoniazid can be successfully treated with a 6-month regimen of rifampin, pyrazinamide, and ethambutol or streptomycin or a 12-month regimen of rifampin and ethambutol. When isoniazid resistance is documented during a 9-month regimen without pyrazinamide, isoniazid should be discontinued. If ethambutol was part of the initial regimen, rifampin and ethambutol should be continued for a minimum of 12 months. If ethambutol was not part of the initial regimen, susceptibility tests should be repeated and two other medications to which the organism is susceptible should be added. Treatment of *M tuberculosis* isolates resistant to agents other than isoniazid and treatment of drug resistance in HIV-infected patients require expert consultation.

Multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis call for an individualized daily DOT plan under the supervision of an experienced clinician. Treatment regimens are based on the patient's overall status and the results of susceptibility studies. Most drug-resistant isolates are resistant to at least isoniazid and rifampin and require a minimum of three drugs to which the organism is susceptible; expert recommendation is often for an intensive five-drug phase of treatment, followed by a two- or three-drug continuation phase of treatment for at least another 12 months. Some experts recommend at least 18–24 months of therapy.

E. Treatment of Extrapulmonary Tuberculosis

In most cases, regimens that are effective for treating pulmonary tuberculosis are also effective for treating extrapulmonary disease. However, many experts recommend

9–12 months of therapy when miliary, meningeal, or bone and joint disease is present. Treatment of skeletal tuberculosis is enhanced by early surgical drainage and debridement of necrotic bone. Corticosteroid therapy has been shown to help prevent constrictive pericarditis from tuberculous pericarditis and to reduce neurologic complications from tuberculous meningitis (Chapter 33).

F. Treatment of Pregnant or Lactating Women

Tuberculosis in pregnancy is usually treated with isoniazid, rifampin, and ethambutol for 2 months, followed by isoniazid and rifampin for an additional 7 months. Ethambutol can be stopped after the first month if isoniazid and rifampin susceptibility is confirmed. Since the risk of teratogenicity with pyrazinamide has not been clearly defined, pyrazinamide should be used only if resistance to other drugs is documented and susceptibility to pyrazinamide is likely. Streptomycin is contraindicated in pregnancy because it may cause congenital deafness. Pregnant women taking isoniazid should receive pyridoxine (vitamin B_6), 10–25 mg orally once a day, to prevent peripheral neuropathy.

Small concentrations of antituberculous drugs are present in breast milk. First-line therapy is not known to be harmful to nursing newborns at these concentrations. Therefore, breastfeeding is not contraindicated while receiving first-line antituberculous therapy. Lactating women receiving other agents should consult a tuberculosis expert.

G. Treatment Monitoring

Adults should have measurements of a CBC (including platelets) and serum bilirubin, hepatic enzymes, BUN, and creatinine before starting therapy for tuberculosis. Visual acuity and red-green color vision tests are recommended before initiation of ethambutol, and serum uric acid is recommended before starting pyrazinamide. Audiometry should be performed if streptomycin therapy is initiated.

Routine monitoring of laboratory tests for evidence of medication toxicity during therapy is not recommended unless baseline results are abnormal or liver disease is suspected. Monthly questioning for symptoms of medication toxicity is advised. Patients should be educated about common side effects of antituberculous medications and instructed to seek medical attention should these symptoms occur. Monthly follow-up of outpatients is recommended, including sputum smear and culture for *M tuberculosis*, until cultures convert to negative. Patients with negative sputum cultures after 2 months of treatment should have at least one additional sputum smear and culture performed at the end of therapy. Patients with drug-resistant isolates should have sputum cultures performed monthly during the entire course of treatment. A chest radiograph at the end of therapy provides a useful baseline for any future comparison.

Patients whose cultures do not become negative or whose symptoms do not resolve despite 3 months of therapy should be evaluated for nonadherence to the regimen and for drug-resistant organisms. DOT is recommended for the remainder of the treatment regimen, and the addition of at least two drugs not previously given should be considered pending repeat drug susceptibility testing. The clinician should seek expert assistance if drug resistance is newly found, if the patient remains symptomatic, or if smears or cultures remain positive.

Patients with only a clinical diagnosis of pulmonary tuberculosis (smears and cultures negative for *M tuberculosis*) whose symptoms and radiographic abnormalities are unchanged after 3 months of treatment usually either have another process or have had tuberculosis in the past.

H. Treatment of Latent Tuberculosis

Treatment of latent tuberculous infection is essential to controlling and eliminating tuberculosis and substantially reduces the risk that infection will progress to active disease. Targeted testing with the tuberculin skin test or interferon gamma release assays is used to identify persons who are at high risk for tuberculosis and who stand to benefit from treatment of latent infection. Table 9–13 gives the tuberculin skin test criteria for treatment of latent tuberculous infection. In general, patients with a positive tuberculin skin test or interferon gamma release assay who are at increased risk for exposure or disease are treated. It is essential that each person who meets the criteria for treatment of latent tuberculous infection undergo a careful assessment to exclude active disease. A history of past treatment for tuberculosis and contraindications to treatment should be sought. All patients at risk for HIV infection should have an HIV test. Patients suspected of having tuberculosis should receive one of the recommended multidrug regimens for active disease until the diagnosis is confirmed or excluded.

Some close contacts of persons with active tuberculosis should be evaluated for treatment of latent tuberculous infection despite a negative tuberculin skin test reaction (less than 5 mm of induration). These include immunosuppressed persons and those in whom disease may develop quickly after tuberculous infection. Close contacts who have a negative tuberculin skin test reaction on initial testing should be retested 10–12 weeks later.

Several treatment regimens for both HIV-negative and HIV-positive persons are available for the treatment of latent tuberculous infection: (1) **Isoniazid:** A 9-month oral regimen (minimum of 270 doses administered within 12 months) is preferable to 6 months of therapy. Dosing options include a daily dose of 300 mg or twice-weekly doses of 15 mg/kg. Persons at risk for developing isoniazid-associated peripheral neuropathy (those with diabetes mellitus, uremia, malnutrition, alcoholism, HIV infection, pregnancy, or seizure disorder) may be given supplemental pyridoxine (vitamin B_6), 10–50 mg/day. (2) **Isoniazid and rifampin:** A 3-month oral regimen of daily isoniazid (300 mg) and rifampin (600 mg). (3) **Isoniazid and rifapentine:** A 3-month oral regimen of once weekly isoniazid at 15 mg/kg and rifapentine at 15–30 mg/kg. (4) **Rifampin:** Patients who cannot tolerate isoniazid can be considered for a 4-month oral regimen of rifampin at 600 mg daily. HIV-positive patients receiving protease inhibitors or NNRTIs who are given rifampin or rifapentine require management by experts in both tuberculosis and HIV disease (see Treatment of Tuberculosis in HIV-Positive Persons, above).

Contacts of persons with isoniazid-resistant, rifampin-sensitive tuberculosis should receive a 2-month regimen of rifampin and pyrazinamide or a 4-month regimen of daily rifampin alone. Contacts of persons with drug-resistant tuberculosis should receive two drugs to which the infecting organism has demonstrated susceptibility. Contacts in whom the tuberculin skin test or interferon gamma release assay is negative and contacts who are HIV seronegative may be observed without treatment or treated for 6 months. HIV-positive contacts should be treated for 12 months. All contacts of persons with multidrug-resistant tuberculosis or extensively drug-resistant tuberculosis should have 2 years of follow-up regardless of type of treatment.

Persons with a positive tuberculin skin test (5 mm or more of induration) and fibrotic lesions suggestive of old tuberculosis on chest radiographs who have no evidence of active disease and no history of treatment for tuberculosis should receive 9 months of isoniazid or 4 months of rifampin (with or without isoniazid). Pregnant or breast-feeding women with latent tuberculosis should receive either daily or twice-weekly isoniazid with pyridoxine (vitamin B_6).

Baseline laboratory testing is indicated for patients at risk for liver disease, patients with HIV infection, women who are pregnant or within 3 months of delivery, and persons who use alcohol regularly. Patients receiving treatment for latent tuberculous infection should be evaluated once a month to assess for symptoms and signs of active tuberculosis and hepatitis and for adherence to their treatment regimen. Routine laboratory testing during treatment is indicated for those with abnormal baseline laboratory tests and for those at risk for developing liver disease.

BCG vaccine is an antimycobacterial vaccine developed from an attenuated strain of *M bovis*. Millions of individuals worldwide have been vaccinated with BCG. The vaccine is not generally recommended in the United States because of the low prevalence of tuberculous infection, the vaccine's interference with the ability to determine latent tuberculous infection using tuberculin skin test reactivity, and its variable effectiveness in prophylaxis of pulmonary tuberculosis. BCG vaccination in the United States should be undertaken only after consultation with local health officials and tuberculosis experts. Vaccination of health care workers should be considered on an individual basis in settings in which a high percentage of tuberculosis patients are infected with strains resistant to both isoniazid and rifampin, in which transmission of such drug-resistant *M tuberculosis* and subsequent infection are likely, and in which comprehensive tuberculous infection-control precautions have been implemented but have not been successful. The BCG vaccine is contraindicated in persons with impaired immune responses due to disease or medications.

Prognosis

Almost all properly treated immunocompetent patients with tuberculosis can be cured. Relapse rates are less than 5% with current regimens. The main cause of treatment failure is nonadherence to therapy.

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PULMONARY DISEASE CAUSED BY NONTUBERCULOUS MYCOBACTERIA

ESSENTIALS OF DIAGNOSIS

- Chronic cough, sputum production, and fatigue; less commonly: malaise, dyspnea, fever, hemoptysis, and weight loss.
- Parenchymal opacities on chest radiograph, most often thin-walled cavities or multiple small nodules associated with bronchiectasis.
- Isolation of nontuberculous mycobacteria in a sputum culture.

General Considerations

Mycobacteria other than *M tuberculosis*—nontuberculous mycobacteria (NTM), sometimes referred to as "atypical" mycobacteria—are ubiquitous in water and soil and have been isolated from tap water. Marked geographic variability exists, both in the NTM species responsible for disease and in the prevalence of disease. These organisms are not considered communicable from person to person, have distinct laboratory characteristics, and are often resistant to most antituberculous medications (Chapter 33). Long-term epidemiologic data suggest that NTM disease has been increasing in the United States.

Definition & Pathogenesis

The diagnosis of lung disease caused by NTM is based on a combination of clinical, radiographic, and bacteriologic criteria and the exclusion of other diseases that can resemble the condition. Specific diagnostic criteria are discussed below. Complementary data are important for diagnosis because NTM organisms can reside in or colonize the airways without causing clinical disease.

Mycobacterium avium complex (MAC) is the most frequent cause of NTM pulmonary disease in humans in the United States. *Mycobacterium kansasii* is the next most frequent pulmonary pathogen. Other NTM causes of pulmonary disease include *Mycobacterium abscessus, Mycobacterium xenopi*, and *Mycobacterium malmoense;* the list of more unusual etiologic NTM species is long. Most NTM cause a chronic pulmonary infection that resembles tuberculosis but tends to progress more slowly. Disseminated disease is rare in immunocompetent persons; however, disseminated MAC disease is common in patients with AIDS.

Clinical Findings

A. Symptoms and Signs

NTM infection among immunocompetent persons frequently presents in one of three prototypical patterns: cavitary, upper lobe lesions in older male smokers that may mimic *M tuberculosis*; nodular bronchiectasis affecting the mid lung zones in middle-aged women with chronic cough; and hypersensitivity pneumonitis following environmental exposure. Most patients with NTM infection experience a chronic cough, sputum production, and fatigue. Less common symptoms include malaise, dyspnea, fever, hemoptysis, and weight loss. Symptoms from coexisting lung disease (COPD, bronchiectasis, previous mycobacterial disease, cystic fibrosis, and pneumoconiosis) may confound the evaluation. In patients with bronchiectasis, coinfection with NTM and *Aspergillus* is a negative prognostic factor. New or worsening infiltrates as well as adenopathy or pleural effusion (or both) are described in HIV-positive patients with NTM infection as part of the immune reconstitution inflammatory syndrome following institution of antiretroviral therapy.

B. Laboratory Findings

The diagnosis of NTM infection rests on recovery of the pathogen from cultures. Sputum cultures positive for atypical mycobacteria do not prove infection because NTM may exist as saprophytes colonizing the airways or may be environmental contaminants. Bronchial washings are considered to be more sensitive than expectorated sputum samples; however, their specificity for clinical disease is not known.

Bacteriologic criteria have been proposed based on studies of patients with cavitary disease with MAC or *M kansasii*. Diagnostic criteria in immunocompetent persons include the following: positive culture results from at least two separate expectorated sputum samples; or positive culture from at least one bronchial wash; or a positive culture from pleural fluid or any other normally sterile site. The diagnosis can also be established by demonstrating NTM cultured from a lung biopsy, bronchial wash, or sputum plus histopathologic changes, such as granulomatous inflammation in a lung biopsy. Rapid species identification of some NTM is possible using DNA probes or high-pressure liquid chromatography.

Diagnostic criteria are less stringent for patients with severe immunosuppression. HIV-infected patients may show significant MAC growth on culture of bronchial washings without clinical infection; therefore, HIV patients being evaluated for MAC infection must be considered individually.

Medication susceptibility testing on cultures of NTM is recommended for the following NTM: (1) *Mycobacterium avium intracellulare* to macrolides only (clarithromycin and azithromycin); (2) *M kansasii* to rifampin; and (3) rapid growers (such as *Mycobacterium fortuitum, Mycobacterium chelonae, and M abscessus*) to amikacin, doxycycline, imipenem, fluoroquinolones, clarithromycin, cefoxitin, and sulfonamides.

C. Imaging

Chest radiographic findings include infiltrates that are progressive or persist for at least 2 months, cavitary lesions, and multiple nodular densities. The cavities are often thin-walled and have less surrounding parenchymal infiltrate than is commonly seen with MTB infections. Evidence of contiguous spread and pleural involvement is often present. High-resolution CT of the chest may show multiple small nodules with or without multifocal bronchiectasis. Progression of pulmonary infiltrates during therapy or lack of radiographic improvement over time are poor prognostic signs and also raise concerns about secondary or alternative pulmonary processes. Clearing of pulmonary infiltrates due to NTM is slow.

Treatment

Establishing NTM infection does not mandate treatment in all cases, for two reasons. First, clinical disease may never develop in some patients, particularly asymptomatic patients with few organisms isolated from single specimens. Second, the spectrum of clinical disease severity is very wide; in patients with mild or slowly progressive symptoms, traditional chemotherapeutic regimens using a combination of agents may lead to drug-induced side effects worse than the disease itself. These features at least partly explain variability of adherence to treatment guidelines in practice.

Specific treatment regimens and responses to therapy vary with the species of NTM. HIV-seronegative patients with MAC pulmonary disease usually receive a combination of daily clarithromycin or azithromycin, rifampin or rifabutin, and ethambutol (Table 9–15). For patients with severe fibrocavitary disease, streptomycin or amikacin is added for the first 2 months. The optimal duration of treatment is unknown, but therapy should be continued for 12 months after sputum conversion. Medical treatment is initially successful in about two-thirds of cases, but relapses after treatment are common; long-term benefit is demonstrated in about half of all patients. Those who do not respond favorably generally have active but stable disease. Surgical resection is an alternative for the patient with progressive disease that responds poorly to chemotherapy. Disease caused by *M kansasii* responds well to drug therapy. A daily regimen of rifampin, isoniazid, and ethambutol for at least 18 months with a minimum of 12 months of negative cultures is usually successful. Rapidly growing

mycobacteria (*M abscessus*, *M fortuitum*, *M chelonae*) are generally resistant to standard antituberculous therapy.

When to Refer

Patients with rapidly growing mycobacteria infection should be referred for expert management.

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PULMONARY NEOPLASMS

See Chapter 39 for discussions of Lung Cancer, Secondary Lung Cancer, and Mesothelioma.

SCREENING FOR LUNG CANCER

Lung cancer remains the leading cause of cancer-related mortality, in large part secondary to advanced stage at diagnosis (Chapter 39). Two large RCTs reported findings in 2011 regarding the utility of lung cancer screening. The Prostate, Lung, Colorectal and Ovarian Randomized Trial (PLCO) randomized 154,901 adults (52% current or former smokers) between the ages of 55 and 74 years to receive either no screening or annual posterior-anterior chest radiographs for 4 consecutive years. The investigators monitored the participants after screening for an average of 12 years. Results showed no mortality benefit from four annual chest radiographs either in the whole cohort or in a subset of heavy smokers who met the entry criteria for the other major trial, the National Lung Screening Trial (NLST). The NLST enrolled 53,454 current or former smokers (minimum 30-pack year exposure history) between the ages of 55 and 74 years who were randomly assigned to one of two screening modalities: three annual posterior-anterior chest radiographs or three annual low-dose chest CT scans. They were monitored for an additional 6.5 years after screening. Compared with chest radiography, low-dose chest CT detected more early-stage lung cancers and fewer advanced-stage lung cancers, indicating that CT screening systematically shifted the time of diagnosis to earlier stages, thereby providing more persons the opportunity for effective treatment. Furthermore, compared with chest radiographs, the cohort that received three annual CT scans had a statistically significant mortality benefit, with reductions in both lung cancer deaths (20.0%) and all-cause mortality (6.7%). This was the first evidence from an RCT demonstrating that lung cancer screening reduced all-cause mortality.

Additional information from PLCO, the NLST, and multiple other ongoing randomized trials is available. Trials in the Netherlands and Belgium (NELSON), Germany (LUSI), Denmark (DLCST), the United Kingdom (UKLS), and Italy (MILD, DANTE, ITALUNG) have been completed. These have revealed variable findings depending on the risk profile of the included patients, but the broad results indicate that screening is most likely to be effective, with reduction in lung cancer-specific mortality, if performed at short intervals in a high-risk population, as was done in NLST. Some studies indicate that the mortality benefit may be higher among women than among men. Issues that remain of concern regarding lung cancer screening include the following: **(1) Generalizability to practice:** NLST-participating institutions demonstrated a high level of expertise in imaging interpretation and diagnostic evaluation. Ninety-six percent of findings on CT were false positives but the vast majority of patients were monitored with serial imaging. Invasive diagnostic evaluations were uncommon and were associated with a low complication rate (1.4%). **(2) Duration of screening:** The rate of detection of new lung cancers did not fall with each subsequent annual screening over 3 years. Since new lung cancers become detectable during each year-long screening interval, the optimal number of annual CT scans is unknown as is the optimal screening interval. **(3) Overdiagnosis:** After 6.4 years of post-screening observation, there were more lung cancers in the NLST CT cohort than the chest radiography cohort (1089 and 969, respectively). Since the groups were randomized and well matched, lung cancer incidence should have been identical. Therefore, 18.5% of the lung cancers detected by CT remained clinically silent and invisible on chest radiograph for 6.4 years. Many, perhaps most, of these lung cancers would never cause clinical disease and represent overdiagnosis. **(4) Cost effectiveness:** Studies in the United States, Canada, and Europe suggest screening for lung cancer is cost effective; however, whether it is cost effective in all countries has not been determined.

In 2021, the USPSTF updated its recommendation for low-dose CT screening. Annual low-dose CT screening for lung cancer is recommended for those at high risk. High-risk criteria include age 50–80 years, at least a 20 pack-year smoking history, and either current smoking or quit date within past 15 years. Screening should be stopped once 15 years have elapsed since quitting smoking, or if a comorbid condition renders the benefits of screening null. Simulation models developed for the purposes of informing this recommendation found yearly screening using these parameters to be the most efficient in reducing lung cancer–related deaths, though more false-positive test results are expected compared to the original recommendation.

All patients participating in a screening program who still smoke should receive smoking cessation interventions.

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SOLITARY PULMONARY NODULE

A solitary pulmonary nodule, sometimes referred to as a "coin lesion," is a less-than-3-cm isolated, rounded opacity on chest imaging outlined by normal lung and not associated with infiltrate, atelectasis, or adenopathy. Most are asymptomatic and represent an incidental finding on chest radiography or CT scanning. The finding is important because it carries a significant risk of malignancy. The frequency of malignancy in surgical series ranges from 10% to 68% depending on patient population. Benign neoplasms, such as hamartomas, account for less than 5% of solitary nodules. Most benign nodules are infectious granulomas.

The goals of evaluation are to identify and resect malignant tumors in patients who will benefit from resection while avoiding invasive procedures in benign disease. The task is to identify nodules with a sufficiently high probability of malignancy to warrant biopsy or resection or a sufficiently low probability of malignancy to justify observation.

Symptoms alone rarely establish the cause, but clinical and imaging data can be used to assess the probability of malignancy. Malignant nodules are rare in persons under age 30. Above age 30, the likelihood of malignancy increases with age. Smokers are at increased risk, and the likelihood of malignancy increases with the number of cigarettes smoked daily. Patients with a prior malignancy have a higher likelihood of having a malignant solitary nodule.

The first step in the imaging evaluation is to review old imaging studies. Comparison with prior studies allows estimation of doubling time, which is an important marker for malignancy. Rapid progression (doubling time less than 30 days) suggests infection, while long-term stability (doubling time greater than 465 days) suggests benignity. Certain radiographic features help in estimating the probability of malignancy. Size is correlated with malignancy. A study of solitary nodules identified by CT scan showed a 1% malignancy rate in those measuring 2–5 mm, 24% in 6–10 mm, 33% in 11–20 mm, and 80% in 21–45 mm nodules. The appearance of a smooth, well-defined edge is characteristic of a benign process. Ill-defined margins or a lobular appearance suggest malignancy. A high-resolution CT finding of spiculated margins and a peripheral halo are both highly associated with malignancy. Calcification and its pattern are also helpful clues. Benign lesions tend to have dense calcification in a central or laminated pattern. Malignant lesions are associated with sparser calcification that is typically stippled or eccentric. Cavitary lesions with thick (greater than 16 mm) walls are much more likely to be malignant. High-resolution CT offers better resolution of these characteristics than chest radiography and is more likely to detect lymphadenopathy or the presence of multiple lesions. Chest CT is indicated for any suspicious solitary pulmonary nodule.

Treatment

Based on clinical and radiologic data, the clinician should assign a specific probability of malignancy to the lesion. The decision whether to recommend a biopsy or surgical excision depends on the interpretation of this probability in light of the patient's unique clinical situation. Quantitative prediction models (Brock model, VA Cooperative model) are available to assess risk of malignancy. The probabilities in parentheses below represent guidelines only and should not be interpreted as definitive.

In the case of solitary pulmonary nodules, a continuous probability function may be grouped into three categories. In patients with a **low probability (less than 5%) of malignancy** (eg, age under 30, lesions stable for more than 2 years, characteristic pattern of benign calcification), watchful waiting is appropriate. Management consists of serial imaging studies at intervals that could identify growth suggestive of malignancy. Three-dimensional reconstruction of high-resolution CT images provides a more sensitive test for growth.

Patients with a **high probability (greater than 60%) of malignancy** should proceed directly to resection following staging, provided the surgical risk is acceptable. Biopsies rarely yield a specific benign diagnosis and are not indicated.

Optimal management of patients with an **intermediate probability of malignancy (5–60%)** remains controversial. The traditional approach is to obtain a diagnostic biopsy, either through bronchoscopy or transthoracic needle aspiration (TTNA). Bronchoscopy yields a diagnosis in 10–80% of procedures depending on the size of the nodule and its location. In general, the bronchoscopic yield for nodules that are less than 2 cm and peripheral is low, although complications are generally rare. Newer bronchoscopic modalities, such as electromagnetic navigation and ultrathin bronchoscopy are being studied, although their impact upon diagnostic yield remains uncertain. TTNA has a higher diagnostic yield, reported to be between 50% and 97%. The yield is strongly operator-dependent, however, and is affected by the location and size of the lesion. Complications are higher than bronchoscopy, with pneumothorax occurring in up to 30% of patients, with up to one-third of these patients requiring placement of a chest tube.

Disappointing diagnostic yields and a high false-negative rate (up to 20–30% in TTNA) have prompted alternative approaches. **PET** detects increased glucose metabolism within malignant lesions with high sensitivity (85–97%) and specificity (70–85%). Many diagnostic algorithms have incorporated PET into the assessment of patients with inconclusive high-resolution CT findings. A positive PET increases the likelihood of malignancy, and a negative PET excludes most cancers. False-negative PET scans can occur with tumors with low metabolic activity

(most notably, carcinoid tumors and adenocarcinomas, particularly minimally invasive or in situ adenocarcinomas), so follow-up CT imaging is typically performed at discrete intervals to ensure absence of growth. PET has several other drawbacks: resolution below 1 cm is poor, the test is expensive, and availability remains limited.

Sputum cytology is highly specific but lacks sensitivity. It is used in central lesions and in patients who are poor candidates for invasive diagnostic procedures.

Some centers recommend **video-assisted thoracoscopic surgery (VATS)** resection of all solitary pulmonary nodules with intermediate probability of malignancy. In some cases, the surgeon will remove the nodule and evaluate it in the operating room with frozen section. If the nodule is malignant, he or she will proceed to lobectomy and lymph node sampling, either thoracoscopically or through conversion to standard thoracotomy. This approach is less common when preoperative PET scanning is available.

All patients should be provided with an estimate of the likelihood of malignancy, and their preferences should be used to help guide diagnostic and therapeutic decisions. A strategy that recommends observation may not be preferred by a patient who desires a definitive diagnosis. Similarly, a surgical approach may not be agreeable to all patients unless the presence of cancer is definitive. Patient preferences should be elicited, and patients should be well informed regarding the specific risks and benefits associated with the recommended approach as well as the alternative strategies.

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RIGHT MIDDLE LOBE SYNDROME

Right middle lobe syndrome is recurrent or persistent atelectasis of the right middle lobe. This collapse is related to the relatively long length and narrow diameter of the right middle lobe bronchus and the oval ("fish mouth") opening to the lobe, in the setting of impaired collateral ventilation. Fiberoptic bronchoscopy or CT scan is often necessary to rule out obstructing tumor. Foreign body or other benign causes are common.

BRONCHIAL CARCINOID TUMORS

Bronchial carcinoid tumors are malignant low- and intermediate-grade neuroendocrine tumors of the lung, with a favorable prognosis compared to high-grade neuroendocrine tumors such as small cell lung cancer. Bronchial carcinoids typically occur as pedunculated or sessile growths in central bronchi. Common symptoms of bronchial carcinoid tumors are hemoptysis, cough, focal wheezing, and recurrent postobstructive pneumonia. Peripherally located bronchial carcinoid tumors are rare and present as asymptomatic solitary pulmonary nodules. **Carcinoid syndrome** (flushing, diarrhea, wheezing, hypotension) and paraneoplastic Cushing syndrome are rare. Fiberoptic bronchoscopy may reveal a pink or purple tumor in a central airway. These lesions have a well-vascularized stroma, and biopsy may be complicated by significant bleeding. CT scanning is helpful to localize the lesion and to follow its growth over time. Octreotide scintigraphy is also available for localization of these tumors.

Bronchial carcinoid tumors grow slowly; the aggressiveness is determined by the cell histology, with "typical carcinoid," a low-grade tumor, demonstrating a more indolent and favorable course than "atypical carcinoid," an intermediate-grade tumor. Bronchial carcinoid tumor staging follows the same TNM classification as other lung cancers. Surgical excision, including lymph node dissection and resection, is recommended for localized disease, and the prognosis is generally favorable. Most bronchial carcinoid tumors respond poorly to radiation and chemotherapy (see Chapter 39).

Adenomas, carcinomas, and other malignancies may rarely metastasize to the bronchi and present with endobronchial lesions. Hamartomas, myxomas, and amyloid are other rarer entities in the differential diagnosis of endobronchial mass lesions.

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MEDIASTINAL MASSES

Various developmental, neoplastic, infectious, traumatic, and cardiovascular disorders may cause masses that appear in the mediastinum on chest radiograph. A useful convention arbitrarily divides the mediastinum into three compartments—anterior, middle, and posterior—in order to classify mediastinal masses and assist in differential diagnosis based on contents of these anatomic regions. The anterior compartment is bounded by the sternum anteriorly and the surface of the great vessels and pericardium posteriorly. The middle compartment extends from the anterior pericardium to the anterior surface of the thoracic spine. The posterior compartment is paravertebral.

Specific mediastinal masses have a predilection for one or more of these compartments; most are located in the anterior or middle compartment.

The differential diagnosis of an **anterior mediastinal mass** includes thymoma, teratoma, thyroid lesions, lymphoma, and mesenchymal tumors (lipoma, fibroma). The differential diagnosis of a **middle mediastinal mass** includes lymphadenopathy, pulmonary artery enlargement, aneurysm of the aorta or innominate artery, developmental cyst (bronchogenic, enteric, pleuropericardial), dilated azygous or hemiazygous vein, and foramen of Morgagni hernia. The differential diagnosis of a **posterior mediastinal mass** includes hiatal hernia, neurogenic tumor, meningocele, esophageal tumor, foramen of Bochdalek hernia, thoracic spine disease, and extramedullary hematopoiesis. The neurogenic tumor group includes neurilemmoma, neurofibroma, neurosarcoma, ganglioneuroma, and pheochromocytoma.

Symptoms and signs of mediastinal masses are nonspecific and are usually caused by the effects of the mass on surrounding structures. Insidious onset of retrosternal chest pain, dysphagia, or dyspnea is often an important clue to the presence of a mediastinal mass. In about half of cases, symptoms are absent, and the mass is detected on routine chest radiograph. Physical findings vary depending on the nature and location of the mass.

CT scanning is helpful in management; additional radiographic studies of benefit include barium swallow if esophageal disease is suspected, Doppler sonography or venography of brachiocephalic veins and the superior vena cava, and angiography. MRI is useful; its advantages include better delineation of hilar structures and distinction between vessels and masses. Tissue diagnosis via either needle or excisional biopsy is generally necessary when a neoplastic process is considered. Treatment and prognosis depend on the underlying cause of the mediastinal mass.

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INTERSTITIAL LUNG DISEASE (Diffuse Parenchymal Lung Disease)

ESSENTIALS OF DIAGNOSIS

- Insidious onset of progressive dyspnea and nonproductive chronic cough.
- Tachypnea, bibasilar dry rales; digital clubbing and right heart failure with advanced disease.
- Chest radiographs with patchy distribution of ground glass, reticular, nodular, reticulonodular, or cystic opacities.
- Reduced lung volumes, pulmonary diffusing capacity, and 6-minute walk distance; hypoxemia with exercise.

Interstitial lung disease, or diffuse parenchymal lung disease, comprises a heterogeneous group of disorders that share common presentations (dyspnea), physical findings (late inspiratory crackles), and chest radiographs (septal thickening and reticulonodular changes).

The term "interstitial" is misleading since the pathologic process usually begins with injury to the alveolar epithelial or capillary endothelial cells (alveolitis). Persistent alveolitis may lead to obliteration of alveolar capillaries and reorganization of the lung parenchyma, accompanied by irreversible fibrosis. The process does not affect the airways proximal to the respiratory bronchioles. Table 9–16 outlines a selected list of differential diagnoses of interstitial lung disease. In most patients, no specific cause can be identified. In the remainder, the principal causes are medications, a variety of organic and inorganic dusts, and connective tissue diseases. The history—particularly the occupational and medication history—may provide evidence of a specific cause. The presence of diffuse parenchymal lung disease in the setting of an established connective tissue disease, such as rheumatoid arthritis, SLE, systemic sclerosis (scleroderma), polymyositis-dermatomyositis, Sjögren syndrome, and other overlap conditions, is suggestive of the cause. In some cases, lung disease precedes the more typical manifestations of the underlying connective tissue disease by months or years.

Known causes of interstitial lung disease are dealt with in their specific sections. The important idiopathic forms are discussed below.

DIFFUSE INTERSTITIAL PNEUMONIAS

ESSENTIALS OF DIAGNOSIS

- Important to identify specific fibrosing disorders.
- Idiopathic disease may require biopsy for diagnosis.
- Accurate diagnosis identifies patients most likely to benefit from therapy.

General Considerations

The most common diagnosis among patients with diffuse interstitial lung disease is one of the interstitial pneumonias, including all the entities described in Table 9–17. Historically, a diagnosis of interstitial lung disease was based on clinical and radiographic criteria with only a small number of patients undergoing surgical lung biopsy. When biopsies were obtained, the common element of

Table 9–16. Differential diagnosis of interstitial lung disease (listed alphabetically within category).

Medication-related
Antiarrhythmic agents (amiodarone)
Antibacterial agents (nitrofurantoin, sulfonamides)
Antineoplastic agents (bleomycin, cyclophosphamide, methotrexate, nitrosoureas)
Antirheumatic agents (gold salts, penicillamine)
Phenytoin
Environmental and occupational (inhalation exposures)
Dust, inorganic (asbestos, beryllium, hard metals, silica)
Dust, organic (thermophilic actinomycetes, avian antigens, *Aspergillus* species)
Gases, fumes, and vapors (chlorine, isocyanates, paraquat, sulfur dioxide)
Ionizing radiation
Talc (injection drug users)
Infections
Fungus, disseminated (*Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum*)
Mycobacteria, disseminated
Pneumocystis jirovecii
Viruses
Primary pulmonary disorders
Cryptogenic organizing pneumonia
Idiopathic interstitial pneumonia: acute interstitial pneumonia, desquamative interstitial pneumonia, nonspecific interstitial pneumonia, usual interstitial pneumonia, respiratory bronchiolitis–associated interstitial lung disease
Pulmonary alveolar proteinosis
Systemic disorders
Acute respiratory distress syndrome
Amyloidosis
Ankylosing spondylitis
Autoimmune disease: dermatomyositis, polymyositis, rheumatoid arthritis, SLE, systemic sclerosis (scleroderma)
Chronic eosinophilic pneumonia
Goodpasture syndrome
Granulomatosis polyangiitis
IBD
Idiopathic pulmonary hemosiderosis
Langerhans cell histiocytosis (eosinophilic granuloma)
Lymphangitic spread of cancer (lymphangitic carcinomatosis)
Lymphangioleiomyomatosis
Pulmonary edema
Pulmonary venous hypertension, chronic
Sarcoidosis

fibrosis led to the grouping together of several histologic patterns under the category of interstitial pneumonia or idiopathic pulmonary fibrosis (IPF). Distinct histopathologic features are now understood to represent different natural histories and responses to therapy (Table 9–17). Therefore, in the evaluation of patients with diffuse interstitial lung disease, clinicians should attempt to identify specific disorders.

Patients with diffuse interstitial pneumonia may have any of the histologic patterns described in Table 9–17. The first step in evaluation is to identify patients whose disease is truly idiopathic. As indicated in Table 9–16, most identifiable causes of diffuse interstitial pneumonia are medication-related, environmental, occupational agent exposure, or infectious. Interstitial lung diseases associated with other systemic disorders (pulmonary renal syndromes, autoimmune disease) may be identified through a careful medical history. Chest radiographs and high-resolution CT scans are diagnostic in some patients. Ultimately, many patients with apparently idiopathic disease require surgical lung biopsy to make a definitive diagnosis.

The importance of accurate diagnosis is twofold. First, it allows the clinician to provide accurate information about the cause and natural history of the illness. Second, accurate diagnosis helps distinguish patients most likely to benefit from therapy.

Clinical Findings

A. Symptoms, Signs, and Imaging

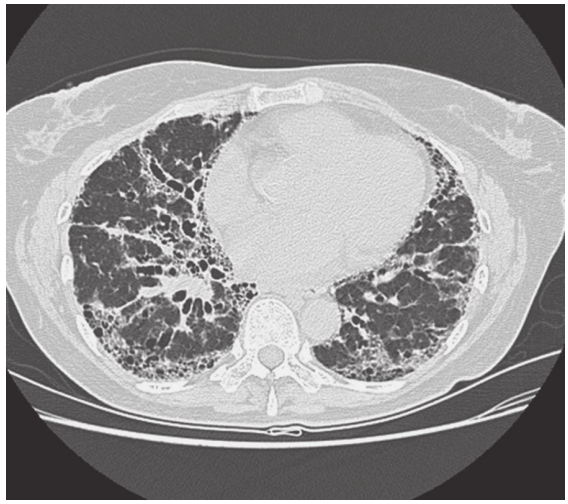
The most common of the diffuse interstitial pneumonias is pulmonary fibrosis associated with the histopathologic pattern of **usual interstitial pneumonia (UIP).** When no associated cause is evident, this is **IPF.** A diagnosis of IPF/UIP can be made in patients who have (1) idiopathic disease by history and inspiratory crackles on physical examination, (2) restrictive physiology on PFTs, and (3) characteristic UIP pattern on high-resolution chest CT (peripheral, basilar predominant opacities associated with honeycombing and traction bronchiectasis) (Figure 9–5). Such patients do not need surgical lung biopsy. Assessment of pulmonary hypertension is recommended in advanced disease.

Table 9–17. Idiopathic interstitial pneumonias.

Name and Clinical Presentation	Histopathology	Radiographic Pattern	Response to Therapy and Prognosis
Usual interstitial pneumonia (UIP) Age 55–60, slight male predominance. Insidious dry cough and dyspnea lasting months to years. Clubbing present at diagnosis in 25–50%. Diffuse fine late inspiratory crackles on lung auscultation. Restrictive ventilatory defect and reduced diffusing capacity on PFTs. ANA and RF positive in ~25% in the absence of documented collagen-vascular disease.	Patchy, temporally and geographically nonuniform distribution of fibrosis, honeycomb change, and normal lung. Type I pneumocytes are lost, and there is proliferation of alveolar type II cells. "Fibroblast foci" of actively proliferating fibroblasts and myofibroblasts. Inflammation is generally mild and consists of small lymphocytes. Intra-alveolar macrophage accumulation is present but is not a prominent feature.	Diminished lung volume. High-resolution CT scanning shows increased linear or reticular bibasilar and subpleural opacities, with associated honeycombing. Unilateral disease is rare. Minimal ground-glass. Areas of normal lung may be adjacent to areas of advanced fibrosis.	No randomized study has demonstrated improved survival compared with untreated patients. Inexorably progressive. Median survival ~3 years, depending on stage at presentation. Nintedanib and pirfenidone reduce rate of decline in lung function. Refer early for lung transplantation evaluation.
Respiratory bronchiolitis–associated interstitial lung disease (RB-ILD)[1] Age 40–45. Presentation like that of UIP though in younger patients. Similar results on PFTs, but less severe abnormalities. Patients with respiratory bronchiolitis are invariably heavy smokers.	Increased numbers of macrophages evenly dispersed within the alveolar spaces. Rare fibroblast foci, little fibrosis, minimal honeycomb change. In RB-ILD the accumulation of macrophages is localized within the peribronchiolar air spaces; in DIP[1], it is diffuse. Alveolar architecture is preserved.	High-resolution CT shows nodular or reticulonodular pattern, more likely to reveal diffuse ground-glass opacities. Honeycombing is rare. May also show upper lobe emphysema.	Spontaneous remission occurs in up to 20% of patients, so natural history unclear. Smoking cessation is essential. Prognosis clearly better than that of UIP: median survival > 10 years. Corticosteroids thought to be effective, but there are no randomized clinical trials to support this view.
Acute interstitial pneumonia (AIP) Clinically known as Hamman-Rich syndrome. Wide age range, many young patients. Acute onset of dyspnea followed by rapid development of respiratory failure. Half of patients report a viral syndrome preceding lung disease. Clinical course indistinguishable from that of idiopathic ARDS.	Pathologic changes reflect acute response to injury within days to weeks. Resembles organizing phase of diffuse alveolar damage. Fibrosis and minimal collagen deposition. May appear like UIP but more homogeneous and there is no honeycomb change—though this may appear if the process persists for more than a month in a patient on mechanical ventilation.	Diffuse bilateral airspace consolidation with areas of ground-glass attenuation on high-resolution CT scan.	Supportive care (mechanical ventilation) critical but effect of specific therapies unclear. High initial mortality: 50–90% die within 2 months after diagnosis. Not progressive if patient survives. Lung function may return to normal or may be permanently impaired.
Nonspecific interstitial pneumonia (NSIP) Age 45–55. Slight female predominance. Like UIP but onset of cough and dyspnea over months, not years.	Nonspecific in that histopathology does not fit into better-established categories. Varying degrees of inflammation and fibrosis, patchy in distribution but uniform in time, suggesting response to single injury. Most have lymphocytic and plasma cell inflammation without fibrosis. Honeycombing present but scant. Some have advocated division into cellular and fibrotic subtypes.	May be indistinguishable from UIP. Most typical picture is bilateral areas of ground-glass attenuation and fibrosis on high-resolution CT. Honeycombing is rare.	Treatment with corticosteroids thought to be effective, but no prospective clinical studies have been published. Overall prognosis good but depends on the extent of fibrosis at diagnosis. Median survival > 10 years.
Cryptogenic organizing pneumonia (COP) Typically age 50–60 but wide variation. Abrupt onset, frequently weeks to a few months following a flu-like illness. Dyspnea and dry cough prominent, but constitutional symptoms are common: fatigue, fever, and weight loss. PFTs usually show restriction, but up to 25% show concomitant obstruction.	Included in the idiopathic interstitial pneumonias on clinical grounds. Buds of loose connective tissue (Masson bodies) and inflammatory cells fill alveoli and distal bronchioles.	Lung volumes normal. Chest radiograph typically shows interstitial and parenchymal disease with discrete, peripheral alveolar and ground-glass infiltrates. Nodular opacities common. High-resolution CT shows subpleural consolidation and bronchial wall thickening and dilation.	Rapid response to corticosteroids in two-thirds of patients. Long-term prognosis generally good for those who respond. Relapses are common.

[1]Includes desquamative interstitial pneumonia (DIP).

ANA, antinuclear antibody; ARDS, acute respiratory distress syndrome; PFTs, pulmonary function tests; RF, rheumatoid factor; UIP, usual interstitial pneumonia.



▲ **Figure 9–5.** Idiopathic pulmonary fibrosis. CT scan of the lungs showing the typical radiographic pattern of idiopathic pulmonary fibrosis, with a predominantly basilar, peripheral pattern of traction bronchiectasis, reticulation, and early honeycombing.

B. Special Studies

Three diagnostic techniques are in common use: BAL, transbronchial biopsy, and surgical lung biopsy, either through an open procedure or using VATS.

BAL may provide a specific diagnosis in cases of infection, particularly with *P jirovecii* or mycobacteria, or when cytologic examination reveals the presence of malignant cells. Additionally, BAL may be diagnostic of eosinophilic pneumonia, Langerhans cell histiocytosis, or alveolar proteinosis.

Transbronchial biopsy through the flexible bronchoscope is easily performed in most patients. The risks of pneumothorax (5%) and hemorrhage (1–10%) are low. However, the tissue specimens recovered are small, sampling error is common, and crush artifact may complicate diagnosis. Transbronchial biopsy can make a definitive diagnosis of sarcoidosis, lymphangitic spread of carcinoma, pulmonary alveolar proteinosis, miliary tuberculosis, and Langerhans cell histiocytosis. However, in IPF, transbronchial biopsy cannot confirm the diagnosis since the histologic diagnosis requires a pattern of changes rather than a single pathognomonic finding. IPF patients generally require surgical lung biopsy.

Surgical lung biopsy is the standard for diagnosis of diffuse interstitial lung disease. Two or three biopsies taken from multiple sites in the same lung, including apparently normal tissue, may yield a specific diagnosis as well as prognostic information regarding the extent of fibrosis versus active inflammation. Patients under age 60 without a specific diagnosis generally should undergo surgical lung biopsy. In older and sicker patients, the risks and benefits must be weighed carefully for three reasons: (1) the morbidity of the procedure can be significant; (2) a definitive diagnosis may not be possible even with surgical lung biopsy; and (3) when a specific diagnosis is made, there may be no effective treatment. Empiric therapy or no treatment may be preferable to surgical lung biopsy in some patients.

Treatment

Patients with diffuse interstitial pneumonia should be treated by a pulmonologist. Clinical experience suggests that patients with RB-ILD, nonspecific interstitial pneumonia (NSIP), or COP (Table 9–17) frequently respond to corticosteroids and should be given a trial of therapy—typically prednisone, 1–2 mg/kg/day for a minimum of 2 months. Corticosteroid therapy is ineffective in patients with IPF and is not recommended. Nintedanib and pirfenidone are approved for the treatment of IPF based on clinical trials in highly selected patients showing a significant reduction in their rate of decline in lung function, but neither agent improved survival or quality of life. The only definitive treatment for IPF is lung transplantation, with a 5-year survival rate estimated at 50%.

When to Refer

- Patients with diffuse interstitial pneumonia should be referred early to a pulmonologist for expert diagnosis and management.
- Patients with IPF should be referred early to a lung transplant program for evaluation.

Gibson CD et al. Comparison of clinical measures among interstitial lung disease (ILD) patients with usual interstitial pneumonia (UIP) patterns on high-resolution computed tomography. Lung. 2020;198:811. [PMID: 32889595]

SARCOIDOSIS

ESSENTIALS OF DIAGNOSIS

- Symptoms related to the lung, skin, eyes, peripheral nerves, liver, kidney, heart.
- Demonstration of noncaseating granulomas in a biopsy specimen.

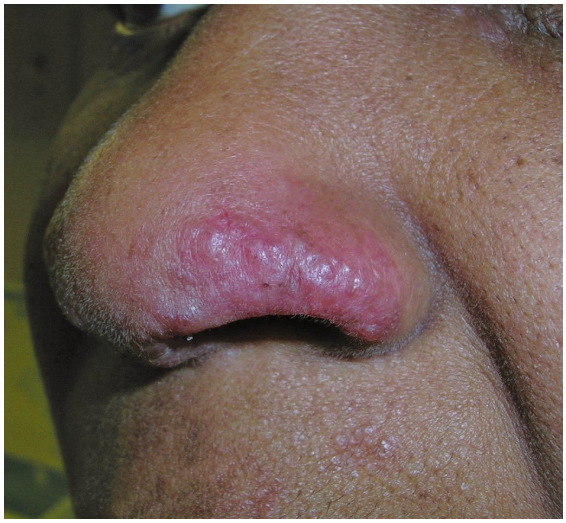
General Considerations

Sarcoidosis is a systemic disease of unknown etiology characterized in about 90% of patients by granulomatous inflammation of the lung. The incidence is highest in North American Black persons and northern European White persons. Among Black persons, women are more frequently affected than men. Onset of disease is usually in the third or fourth decade.

Clinical Findings

A. Symptoms and Signs

Patients may have malaise, fever, and dyspnea of insidious onset. Symptoms caused by skin involvement (erythema nodosum, lupus pernio [Figure 9–6]), iritis, peripheral



▲ **Figure 9–6. Skin involvement in sarcoidosis (lupus pernio), here involving the nasal rim.** (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

neuropathy, arthritis (Chapter 20), or cardiomyopathy may also prompt the patient to seek care. Some individuals are asymptomatic and come to medical attention after abnormal findings on chest radiographs (typically bilateral hilar and paratracheal lymphadenopathy). Physical findings of interstitial lung disease with crackles are uncommon. Other symptoms and findings may include parotid gland enlargement, hepatosplenomegaly, and lymphadenopathy.

B. Laboratory Findings

Laboratory tests may show leukopenia, an elevated ESR, and hypercalcemia (about 5% of patients) or hypercalciuria (20%). ACE levels are elevated in 40–80% of patients with active disease, though this finding is neither sensitive nor specific. Physiologic testing may reveal evidence of airflow obstruction or restriction with decreased lung volumes and diffusing capacity, or both. ECG may show heart block and dysrhythmias.

C. Imaging

Radiographic findings are variable and include bilateral hilar adenopathy alone (radiographic stage I), hilar adenopathy and parenchymal involvement (radiographic stage II), parenchymal involvement alone (radiographic stage III), or advanced fibrotic changes principally in the upper lobes (radiographic stage IV). Parenchymal involvement is usually manifested radiographically by diffuse reticular infiltrates, but focal infiltrates, acinar shadows, nodules, and, rarely, cavitation may be seen. Pleural effusion is noted in less than 10% of patients.

D. Special Examinations

The diagnosis of sarcoidosis generally requires histologic demonstration of noncaseating granulomas in biopsies from a patient with other typical associated manifestations. Other granulomatous diseases (eg, berylliosis, tuberculosis, fungal infections) and lymphoma must be excluded. Biopsy of easily accessible sites (eg, palpable lymph nodes, skin lesions, or salivary glands) may be an initial step. Transbronchial lung biopsy has a high yield (75–90%) as well, especially in patients with radiographic evidence of parenchymal involvement. Some clinicians believe that tissue biopsy is not necessary when stage I radiographic findings are detected in a clinical situation that strongly favors the diagnosis of sarcoidosis (eg, a young Black woman with erythema nodosum). Biopsy is essential whenever clinical and radiographic findings suggest the possibility of an alternative diagnosis, such as lymphoma. BAL fluid in sarcoidosis is usually characterized by an increase in lymphocytes and a high CD4/CD8 cell ratio, but it does not establish a diagnosis. Patients require a yearly ophthalmologic evaluation, liver and renal function testing, PFTs, and an ECG. Cardiac MRI is favored over PET scan for patients with suspected cardiac involvement. Assessment of pulmonary hypertension is recommended in advanced disease.

Treatment

Treatment is not recommended for asymptomatic disease. Oral corticosteroids (prednisone, 0.5–1.0 mg/kg/day) are indicated for patients with disabling constitutional symptoms, hypercalcemia, iritis, uveitis, arthritis, CNS involvement, cardiac involvement, granulomatous hepatitis, cutaneous lesions other than erythema nodosum, and progressive pulmonary lesions. Long-term therapy is usually required over months to years. Immunosuppressive medications, most commonly methotrexate, azathioprine, or infliximab, are used in patients who are intolerant of corticosteroids or who have corticosteroid-refractory disease. A favorable response is defined by a decrease in symptoms, reduction of radiographic abnormalities, and improvement in PFTs.

Prognosis

The outlook is best for patients with hilar adenopathy alone; radiographic involvement of the lung parenchyma is associated with a worse prognosis. Erythema nodosum portends a good outcome. About 20% of patients with lung involvement suffer irreversible lung impairment, characterized by progressive fibrosis, bronchiectasis, and cavitation. Pneumothorax, hemoptysis, mycetoma formation in lung cavities, pulmonary hypertension, and respiratory failure may often complicate this advanced stage. Myocardial sarcoidosis occurs in about 5% of patients, sometimes leading to restrictive cardiomyopathy, cardiac dysrhythmias, and conduction disturbances. Death from respiratory insufficiency occurs in about 5% of patients. Patients require long-term follow-up.

Crouser ED et al. Diagnosis and detection of sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020;201:e26. [PMID: 32293205]
Grunewald J et al. Sarcoidosis. Nat Rev Dis Primers. 2019;5:45. [PMID: 31273209]

Llanos O et al. Sarcoidosis. Med Clin North Am. 2019;103:527. [PMID: 30955519]
Ungprasert P et al. Clinical manifestations, diagnosis, and treatment of sarcoidosis. Mayo Clin Proc Innov Qual Outcomes. 2019;3:358. [PMID: 31485575]

PULMONARY ALVEOLAR PROTEINOSIS

Pulmonary alveolar proteinosis is a rare disease characterized by accumulation of lipoproteinaceous material within alveolar spaces. The condition may be primary (idiopathic) or secondary (occurring in immunodeficiency; hematologic malignancies; inhalation of mineral dusts; or following lung infections, including tuberculosis and viral infections). Progressive dyspnea is the usual presenting symptom. Chest radiograph shows bilateral alveolar infiltrates, and chest CT features a characteristic "crazy-paving" that refers to ground-glass opacities with superimposed interlobular and intralobular septal thickening. The diagnosis is based on demonstration of characteristic findings on BAL (milky appearance and periodic acid-Schiff [PAS]-positive lipoproteinaceous material) in association with clinical and radiographic features. In secondary disease, an elevated anti-GM-CSF (anti-granulocyte-macrophage colony-stimulating factor) titer in serum or BAL fluid is highly sensitive and specific.

The course of the disease varies. Some patients experience spontaneous remission; others develop progressive respiratory insufficiency. Therapy for alveolar proteinosis consists of periodic whole-lung lavage. Patients who cannot tolerate whole lung lavage or who fail to respond may benefit from inhalational or subcutaneous GM-CSF. Pulmonary infection with *Nocardia* or fungi may occur.

Salvaterra E et al. Pulmonary alveolar proteinosis: from classification to therapy. Breathe (Sheff). 2020;16:200018. [PMID: 32684997]
Trapnell BC et al. Pulmonary alveolar proteinosis. Nat Rev Dis Primers. 2019;5:16. [PMID: 30846703]
Trapnell BC et al; IMPALA Trial Investigators. Inhaled molgramostim therapy in autoimmune pulmonary alveolar proteinosis. N Engl J Med. 2020;383:1635. [PMID: 32897035]

EOSINOPHILIC PULMONARY SYNDROMES

Eosinophilic pulmonary syndromes are a diverse group of disorders typically characterized by peripheral blood eosinophilia (typically > 500 cells/mcL [0.5 × 10^9/L]), eosinophilic pulmonary infiltrates, dyspnea, and cough. Many patients have constitutional symptoms, including fever. Common causes include exposure to medications (nitrofurantoin, phenytoin, ampicillin, acetaminophen) or infection with helminths (eg, *Ascaris*, hookworms, *Strongyloides*) or filariae (eg, *Wuchereria bancrofti, Brugia malayi*, tropical pulmonary eosinophilia). **Löffler syndrome** refers to acute eosinophilic pulmonary infiltrates in response to transpulmonary passage of helminth larvae. Pulmonary eosinophilia can also be a feature of other illnesses, including ABPA, eosinophilic granulomatosis with polyangiitis, systemic hypereosinophilic syndromes, eosinophilic granuloma of the lung (properly referred to as pulmonary Langerhans cell histiocytosis), neoplasms, and numerous interstitial lung diseases. If an extrinsic cause is identified, therapy consists of removal of the offending medication or treatment of the underlying parasitic infection.

One-third of cases are idiopathic, and there are two common syndromes. **Acute eosinophilic pneumonia** is an acute, febrile illness characterized by cough and dyspnea, sometimes rapidly progressing to respiratory failure. The chest radiograph is abnormal but nonspecific. BAL fluid frequently shows eosinophilia, but peripheral blood eosinophilia is rare at the onset of symptoms. The response to corticosteroids is usually dramatic. **Chronic eosinophilic pneumonia** has a subacute-chronic presentation, characterized by fever, night sweats, weight loss, and dyspnea. Asthma or atopy is present in half of cases. Chest radiographs often show peripheral infiltrates, the "photographic negative" of pulmonary edema. BAL typically has a marked eosinophilia, and peripheral blood eosinophilia is present in greater than 80%. Therapy with oral prednisone (1 mg/kg/day for 1–2 weeks, followed by a gradual taper over months) usually results in dramatic improvement; however, most patients require at least 10–15 mg of prednisone every other day for a year or more (sometimes indefinitely) to prevent relapses.

Rosenberg CE et al. Approach to eosinophilia presenting with pulmonary symptoms. Chest. 2021;159:507. [PMID: 33002503]
Suzuki Y et al. Eosinophilic pneumonia: a review of the previous literature, causes, diagnosis, and management. Allergol Int. 2019;68:413. [PMID: 31253537]

DISORDERS OF THE PULMONARY CIRCULATION

PULMONARY VENOUS THROMBOEMBOLISM

ESSENTIALS OF DIAGNOSIS

- Third most common cardiovascular cause of death in the United States.
- May present with one or more of the following: dyspnea, pleuritic chest pain, hemoptysis, syncope.
- Tachypnea, tachycardia, hypoxia may be present (alone or in any combination).
- Risk stratification with clinical scores, cardiac biomarkers, and right ventricular imaging is key for management.

General Considerations

Pulmonary venous thromboembolism (VTE), often referred to as PE, is a common, serious, and potentially fatal result of thrombus formation within the deep venous circulation that then migrates to the pulmonary circulation. PE is the third leading cause of death among hospitalized patients. Management demands a vigilant systematic

approach to diagnosis and an understanding of risk factors so that appropriate therapy can be initiated.

Many substances can embolize to the pulmonary circulation, including air (during neurosurgery, from central venous catheters), amniotic fluid (during active labor), fat (long bone fractures), foreign bodies (talc in injection drug users), parasite eggs (schistosomiasis), septic emboli (acute infective endocarditis), and tumor cells (renal cell carcinoma). The most common embolus is thrombus, which may arise anywhere in the venous circulation or right heart but most often originates in the deep veins of the lower extremities. Pulmonary emboli will develop in 50–60% of patients with proximal DVT; half of these embolic events will be asymptomatic. Approximately 50–70% of patients who have symptomatic pulmonary emboli will have lower extremity DVT when evaluated.

Risk factors for PE include venous stasis, injury to the vessel wall, and hypercoagulability (Virchow triad). Venous stasis increases with immobility (obesity, stroke, bed rest—especially postoperative), hyperviscosity (polycythemia), and increased central venous pressures (low cardiac output states, pregnancy). Vessels may be damaged by prior episodes of thrombosis, orthopedic surgery, or trauma. Hypercoagulability can be caused by medications (oral contraceptives, hormonal replacement therapy) or disease (malignancy, surgery) or may be the result of inherited gene defects (factor V Leiden, prothrombin mutation) or acquired thrombophilias (protein C and protein S deficiency, antithrombin deficiency, antiphospholipid antibodies).

PE has multiple physiologic effects. Thrombus occlusion of greater than 20–25% of vascular bed causes right ventricular dilation or dysfunction and increased pulmonary vascular resistance. Vascular obstruction increases physiologic dead space (wasted ventilation) and leads to hypoxemia through right-to-left shunting, decreased cardiac output, and surfactant depletion causing atelectasis.

Clinical Findings

A. Symptoms and Signs

The clinical diagnosis of PE is notoriously challenging because the clinical symptoms and signs are similar to those of other cardiopulmonary conditions. Dyspnea and chest pain on inspiration are common. Diagnosis primarily relies on clinical prediction scores to calculate the pretest probability of PE. Wells score is most commonly used and quantifies clinical risk assessment, allowing separation of patients into low, intermediate, or high probability groups, or PE-likely versus PE-unlikely groups (Table 9–18).

B. Laboratory Findings

The **ECG** is abnormal in 70% of patients with PE. However, the most common abnormalities are sinus tachycardia and nonspecific ST and T wave changes, each seen in approximately 40% of patients. Five percent or less of patients in the PIOPED I study had P pulmonale, right ventricular hypertrophy, right axis deviation, and right bundle branch block.

ABGs usually reveal acute respiratory alkalosis due to hyperventilation and may show hypoxemia.

Table 9–18. Clinical prediction rule for PE.

Variable	Points
Clinical symptoms and signs of DVT (leg swelling and pain with palpation of deep veins)	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate > 100 beats/minute	1.5
Immobilization for > 3 days or surgery in previous 4 weeks	1.5
Previous PE or DVT	1.5
Hemoptysis	1.0
Cancer (with treatment within past 6 months or palliative care)	1.0
Add **Points** *to determine* **Score**, *then refer to* **probability assessments** *below*:	
Three-tiered clinical probability assessment (Wells criteria)	**Score**
High	> 6.0
Moderate	2.0 to 6.0
Low	< 2.0
Dichotomous clinical probability assessment (Modified Wells criteria)	**Score**
PE likely	> 4.0
PE unlikely	< or = 4.0

Data from Wells PS et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the models' utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83:416.

Plasma levels of **D-dimer,** a degradation product of cross-linked fibrin, are elevated in the presence of thrombus. A D-dimer of less than 500 ng/mL may be used to exclude the diagnosis of PE in those patients who have low pretest probability of PE or are PE-unlikely on Wells score. Additionally, an age-adjusted D-dimer value has increased specificity than the usually specified cutoff. Due to much higher false-positive rates, D-dimer is not useful for hospital inpatients.

Serum troponin I, troponin T, and plasma BNP levels are elevated in approximately 25% of patients with PE and are useful in the risk stratification of PE because they correlate with adverse outcomes, including mechanical ventilation, prolonged hospitalization, and death.

C. Imaging and Special Examinations

1. Chest radiography—The chest radiograph is necessary to exclude other common lung diseases, but it does not establish the diagnosis of PE by itself. The chest radiograph may be normal or may show atelectasis, parenchymal infiltrates, and pleural effusions. A prominent central pulmonary artery with local oligemia (Westermark sign) or pleural-based areas of increased opacity that represent intraparenchymal hemorrhage (Hampton hump) are uncommon. Profound hypoxia with a normal chest radiograph is highly suspicious for PE.

2. Pulmonary CT-angiography—Helical CT-PA is the gold standard diagnostic study in North America for suspected PE due to its high sensitivity and specificity as well as wide availability across hospitals. CT-PA requires administration of intravenous radiocontrast dye but is otherwise noninvasive. Patients with intermediate- or high-pretest probability of PE (or PE-likely) or those with an elevated D-dimer should undergo a CT-PA.

3. Ventilation-perfusion ($\dot{V}/\dot{Q}$) lung scanning—$\dot{V}/\dot{Q}$ scanning may be used as an alternative to CT-PA in patients in whom contrast is contraindicated, such as severe contrast-induced anaphylaxis or kidney dysfunction. $\dot{V}/\dot{Q}$ scanning is performed by injecting radiolabeled microaggregated albumin into the venous system, allowing the particles to embolize to the pulmonary capillary bed (perfusion); the patient breathes a radioactive gas or aerosol while the distribution of radioactivity in the lungs is recorded (ventilation). A defect in perfusion without a corresponding defect in ventilation may indicate a PE but is not specific for the diagnosis. A normal $\dot{V}/\dot{Q}$ scan excludes the diagnosis of clinically significant PE (negative predictive value of 91% in the PIOPED I study).

4. Venous thrombosis studies—Venous ultrasonography is the test of choice to detect proximal DVT. Inability to compress the common femoral or popliteal veins in symptomatic patients is diagnostic (positive predictive value of 97%); full compressibility of both sites excludes proximal DVT (negative predictive value of 98%).

Contrast venography may be used to diagnose intraluminal filling defects, though the test is very infrequently used except in complex situations when there is discrepancy between clinical suspicion and venous ultrasound results.

5. Pulmonary angiography—Pulmonary angiography is the historical reference standard for the diagnosis of PE. At present, pulmonary angiography is only used during catheter-directed therapy (for administration of a thrombolytic or for mechanical thrombectomy) in the treatment of acute PE or to confirm the diagnosis of chronic PE in chronic thromboembolic pulmonary hypertension.

Integrated Approach to Diagnosis of Pulmonary Embolism

The diagnosis of PE uses the clinical likelihood derived from clinical prediction rules, such as Wells score (Table 9–18) along with the results of diagnostic tests, such as D-dimer, to establish a pretest probability of PE. The ideal diagnostic approach is a cost-effective, stepwise sequence to come to these decision points at minimal risk to the patient.

In patients with low pretest probability, a normal D-dimer rules out presence of PE. The Pulmonary Embolism Rule-out Criteria (PERC) may be used to identify patients for whom no testing is indicated (Table 9–19). Imaging is recommended for patients with low or intermediate pretest probability (or PE-unlikely) but a positive D-dimer or those with high pretest probability (or PE-likely).

Table 9–19. Pulmonary embolism rule-out criteria (PERC) for low-risk patients.

For patients with a Modified Wells Score ≤ 4[1] who meet ALL of the following criteria, PE is excluded, monitor off anticoagulation, and search for alternative diagnoses.
• Age < 50 years
• Heart rate < 100 bpm
• Oxyhemoglobin saturation on room air ≥ 95%
• No prior history of venous thromboembolism
• No recent (within 4 weeks) trauma or surgery requiring hospitalization
• No presenting hemoptysis
• No estrogen therapy
• No unilateral leg swelling

[1]See Table 9–18.

Data from Kline JA et al. Impact of a rapid rule-out protocol for pulmonary embolism on the rate of screening, missed cases, and pulmonary vascular imaging in an urban US emergency room. Ann Emerg Med. 2004;44:490.

Risk Stratification of Pulmonary Embolism

After a PE diagnosis is made, the next step is risk stratification since this will guide management. There are three categories based on mortality data: high-risk PE, intermediate-risk PE, and low-risk PE. Patients with high-risk PE, also known as massive PE, have hemodynamic compromise, defined as systolic blood pressure less than 90 mm Hg or a systolic blood pressure drop by 40 mm Hg or more for longer than 15 minutes, requiring a vasopressor, or causing a cardiac arrest. Patients with an intermediate-risk PE, also known as submassive PE, are hemodynamically stable but do have signs of right ventricular strain or dysfunction, either by imaging (CT-PA or echocardiogram) or cardiac biomarkers (troponin or BNP). Patients with low-risk PE have normotension without signs of right ventricular dysfunction.

PE severity scores, such as PE Severity Score Index (PESI) or the simplified PESI, compile useful patient characteristics that predict patient outcome. Such scores may also be used to decide which patients may be appropriate for outpatient PE treatment. Imaging of the right ventricle, usually using CT-PA or echocardiogram and cardiac biomarkers (troponin and/or BNP) are other useful tools that may help predict adverse outcomes.

Prevention

Discussion of strategies for the prevention of VTE can be found in Chapter 14.

Treatment

A. Anticoagulation

Anticoagulation is the mainstay therapy for VTE. It impedes additional thrombus formation, allowing endogenous fibrinolytic mechanisms to lyse existing clot, thereby decreasing mortality and recurrence of PE. Initiation of anticoagulation should be considered even prior to a

confirmed diagnosis when there is high clinical suspicion and low risk of bleeding.

Unfractionated heparin binds to and accelerates the ability of antithrombin to inactivate thrombin, factor Xa, and factor IXa. Compared to unfractionated heparin, low-molecular-weight heparins (LMWHs) are as effective but have faster therapeutic activity in the treatment of VTE. Direct-acting oral anticoagulants (DOACs) offer predictable pharmacokinetics and pharmacodynamics with fixed dosing, few drug interactions, and relatively short half-life. DOACs are recommended as first-line anticoagulation for most patients.

The optimal duration of anticoagulation therapy for venous thromboembolism depends on the risk factors for VTE recurrence. Extended anticoagulation should be considered for patients with no identifiable risk factor for the index PE event, those with a persistent risk factor, those with recurrent VTE, or those with a minor risk factor (such as immobility due to prolonged car or air travel, obesity, pregnancy, or increased age). However, those with major transient/reversible risk factors (such as fracture of lower limb; hip or knee surgery; or hospitalization for heart failure, atrial fibrillation, or MI) may be considered for discontinuation of anticoagulation after 3 months. Additionally, duration of therapy needs to take into consideration the patient's age, likelihood and potential consequences of hemorrhage, and preferences for continued therapy. The D-dimer level measured a month after stopping anticoagulant therapy as well as the patient's sex may influence whether to remain off or to restart treatment. In patients who continue taking extended anticoagulation, an annual risk-benefit assessment of continuing anticoagulation therapy should be done.

The major complication of anticoagulation is hemorrhage. Risk factors for hemorrhage include the intensity of the anticoagulation; duration of therapy; concomitant administration of medications, such as aspirin, that interfere with platelet function; and patient characteristics, particularly increased age, previous GI hemorrhage, and coexistent kidney or liver disease.

B. Thrombolytic Therapy

Streptokinase, urokinase, and recombinant tissue plasminogen activator (rt-PA; alteplase) increase plasmin levels and thereby directly lyse intravascular thrombi accelerating resolution of emboli. Guidelines support systemic thrombolysis for high-risk or massive PE (hemodynamically unstable) with low risk of bleeding. Intermediate-risk or submassive PE patients (hemodynamically stable with evidence of right heart strain) do not have a mortality benefit with thrombolytic therapy but do have a significant decrease in incidence of hemodynamic collapse; however, they also have an increase in major hemorrhagic complications, including intracranial hemorrhage. Absolute contraindications to thrombolytic therapy include active bleeding and stroke within the past 3 months. Relative contraindications include uncontrolled hypertension and surgery or trauma within the past 4 weeks.

Catheter-directed thrombolysis delivers a low-dose of the thrombolytic agent directly into the PE, thereby reversing right ventricular dilation faster than anticoagulation alone. This procedure may be considered for patients with high-risk PE (though with higher risks of bleeding) and for those with intermediate-risk PE at increased risk of hemodynamic collapse.

C. Additional Measures

Mechanical pulmonary embolectomy or surgical embolectomy may be considered for selected patients with contraindications to thrombolysis or failure of thrombolysis.

Inferior vena cava filters should be inserted in patients with contraindications to anticoagulation and those with recurrent PE despite adequate anticoagulation. Consideration should be given for those with acute PE and presence of free-floating proximal end DVT, since it carries an increased risk of embolization. Once placed, it must be assessed for removal at the earliest opportunity.

Prognosis

PE is estimated to cause more than 50,000–100,000 deaths annually in the United States. The outlook for most patients is generally good. However, mortality for intermediate-risk (submassive) PE or high-risk (massive) PE may be as high as 20% and 50%, respectively. Therefore, early diagnosis and risk stratification are key. Survivors may have long-term sequelae of PE, such as exercise intolerance, chronic thromboembolic disease, and chronic thromboembolic pulmonary hypertension. Therefore, follow-up care to assess whether patients have persistent or recurrent symptoms is very important.

When to Admit

Most patients with acute PE require hospitalization. The decision to admit patients with acute PE requires assessment of factors placing them at high risk, including their severity of illness (eg, severe hypoxemia), comorbidities (eg, DVT, cardiac dysfunction), educational needs (eg, lack of knowledge about PE and its management), and/or problematic social situations (eg, prior noncompliance with follow-up care). Carefully selected patients with low-risk PE can be safely and effectively managed as outpatients with the aid of integrated clinical decision support systems.

Konstantinides SV et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41:543. [PMID: 31473594]

Rivera-Lebron BN et al. Diagnosis, treatment and follow up of acute pulmonary embolism: consensus statement from the PERT Consortium. Clin Appl Hemost. 2019;25: 1076029619853037. [PMID: 31185730]

Stevens SM et al. Antithrombotic therapy for VTE disease: second update of the CHEST Guideline and Expert Panel Report. Chest. 2021;160:e545. [PMID: 34352278]

PULMONARY HYPERTENSION

ESSENTIALS OF DIAGNOSIS

- Dyspnea, fatigue, chest pain, and syncope on exertion.
- Narrow splitting of second heart sound with loud pulmonary component; findings of right ventricular hypertrophy and heart failure in advanced disease.
- Electrocardiographic evidence of right ventricular strain or hypertrophy and right atrial enlargement.
- Enlarged central pulmonary arteries on chest radiograph.
- Elevated right ventricular systolic pressure, right ventricular dilation or dysfunction on two-dimensional echocardiography with Doppler flow studies.

General Considerations

Pulmonary hypertension is a complex problem characterized by pathologic elevation in pulmonary arterial pressure. Normal pulmonary artery systolic pressure at rest is 15–30 mm Hg, with a mean pressure less than 20 mm Hg. The pulmonary circulation is a low-pressure, low-resistance system due to its large cross-sectional area, and it can accommodate significant increase in blood flow during exercise. The primary pathologic mechanism in pulmonary hypertension is an increase in pulmonary vascular resistance that leads to an increase in the pulmonary systolic pressure. Pulmonary hypertension is defined by a mean pulmonary arterial pressure of 20 mm Hg or more on a resting cardiac catheterization.

The WHO/New York Heart Association (NYHA) functional class currently classifies pulmonary hypertension based on similarities in pathologic mechanisms and includes the following five groups.

Group 1 (pulmonary arterial hypertension [PAH]): This group gathers diseases that localize directly to the pulmonary arteries leading to structural changes, smooth muscle hypertrophy, and endothelial dysfunction. This group includes idiopathic (formerly primary) PAH; heritable PAH; drug- and toxin-induced PAH; PAH associated with HIV infection, portal hypertension, connective tissue disorders (most commonly scleroderma), congenital heart disease, and schistosomiasis; and PAH with features of veno-occlusive disease and pulmonary capillary hemangiomatosis. PAH is defined on a resting cardiac catheterization by a mean pulmonary arterial pressure of 20 mm Hg or more with a pulmonary capillary wedge pressure of 15 mm Hg or less and a pulmonary vascular resistance of 3 Wood units or more.

Group 2 (pulmonary venous hypertension due to left heart disease): This group includes LV systolic or diastolic dysfunction and valvular heart disease.

Group 3 (pulmonary hypertension due to lung disease or hypoxemia): This group is caused by advanced obstructive and restrictive lung disease, including COPD, interstitial lung disease, pulmonary fibrosis as well as other causes of chronic hypoxemia, such as sleep-disordered breathing, alveolar hypoventilation syndromes, and high-altitude exposure.

Group 4 (pulmonary hypertension due to pulmonary obstruction): This group primarily includes chronic thromboembolic pulmonary hypertension but also includes other causes of pulmonary obstructions, such as sarcoma, metastatic malignancies, and congenital pulmonary artery stenosis.

Group 5 (pulmonary hypertension secondary to unclear or multifactorial mechanisms): These patients have pulmonary hypertension secondary to hematologic disorders (eg, chronic hemolytic anemia, sickle cell anemia, myeloproliferative disorders, splenectomy), systemic disorders (eg, sarcoidosis, vasculitis, pulmonary Langerhans cell histiocytosis, neurofibromatosis type 1), metabolic disorders (eg, glycogen storage disease, Gaucher disease, thyroid disease), and miscellaneous causes (eg, ESKD with or without hemodialysis, fibrosing mediastinitis).

The clinical severity of pulmonary hypertension is classified according to the NYHA classification system, which was originally developed for heart failure but subsequently modified by the WHO; it is based primarily on symptoms and functional status.

Class I: No limitation of physical activity; no dyspnea, fatigue, chest pain, or near syncope is present with exertion.

Class II: Slight limitation of physical activity; no symptoms at rest, but ordinary physical activity causes dyspnea, fatigue, chest pain, or near syncope.

Class III: Marked limitation of physical activity; no symptoms at rest, but less than ordinary activity causes dyspnea, fatigue, chest pain, or near syncope.

Class IV: Inability to perform any physical activity without symptoms; dyspnea and fatigue are present at rest and symptoms worsen with any activity.

Clinical Findings

A. Symptoms and Signs

There are no specific symptoms or signs of pulmonary hypertension, which may delay its diagnosis and significantly affect its mortality. Typical symptoms include dyspnea with exertion and with advanced disease, at rest. Patients may have chest pain, nonproductive cough, and fatigue. Syncope may occur with exertion when there is insufficient cardiac output or if there is an arrhythmia.

Findings on physical examination can include jugular venous distention, accentuated pulmonary valve component of the second heart sound, right-sided third heart sound, tricuspid regurgitation murmur, hepatomegaly, and lower extremity edema.

B. Laboratory Findings

Routine blood work is often normal. BNP or pro-BNP may be elevated. All patients should be evaluated for HIV, liver dysfunction, and connective tissue disorders.

The ECG is typically normal except in advanced disease, where right ventricular hypertrophy (right axis deviation, incomplete right bundle branch block) and right atrial enlargement (peaked P wave in the inferior and right-sided leads) can be noted.

C. Imaging and Special Examinations

Radiographs and CT scans of the chest are useful in diagnosis. Enlargement of the right and left main pulmonary arteries is common; right ventricular and right atrial enlargement is seen in advanced disease. Chest CT scanning and PFTs are also useful in determining the cause of pulmonary hypertension for patients in Group 3 (pulmonary hypertension due to lung disease). On PFTs, the combination of normal FVC on spirometry, normal TLC on lung volume measurement, and significantly decreased diffusing capacity may be suggestive of PAH (Group 1). However, FVC and TLC may be also reduced in pulmonary hypertension due to lung disease (Group 3).

Echocardiography is the best screening study. Right ventricular assessment is made by measuring right ventricular size and function as well as right ventricular systolic pressure, which is estimated based on tricuspid jet velocity and right atrial pressure. Additionally, the echocardiogram is useful for assessing underlying cardiac disease (eg, pulmonary hypertension due to left heart disease).

Right-sided cardiac catheterization remains the gold standard for the diagnosis and quantification of pulmonary hypertension and should be performed prior to initiation of advanced therapies. Estimated pressures on echocardiogram correlate with right heart catheterization measurement but can vary by at least 10 mm Hg in more than 50% of cases so should not be used to direct therapy. Cardiac catheterization is particularly helpful in differentiating PAH from pulmonary venous hypertension by assessment of the drop in pressure across the pulmonary circulation, also known as the transpulmonary gradient. A vasodilator challenge can be performed during right heart catheterization and a significant acute vasodilator response consists of a drop in mean pulmonary pressure of greater than 10 mm Hg (or 20%) to less than 40 mm Hg.

In all patients, especially those with a history of PE or risk factors for thromboembolic disease, chronic thromboembolic pulmonary hypertension (Group 4) should be excluded prior to diagnosing idiopathic pulmonary hypertension with $\dot{V}/\dot{Q}$ lung scanning. If abnormal, CT-PA or pulmonary angiography is the next step in confirming the diagnosis and establishing the distribution and extent of disease.

Treatment

Advanced therapies, such as pulmonary vasodilators, are available to treat pulmonary hypertension. Such therapies are chosen based on the patient's functional status according to the NYHA/WHO classification. The mechanisms of action for pulmonary vasodilators follow three main pathways: (1) the nitric oxide pathway: phosphodiesterase inhibitors (sildenafil, tadalafil) and soluble guanylate cyclase stimulators (riociguat); (2) the endothelin pathway: endothelin receptor antagonists (bosentan, ambrisentan, macitentan); and (3) the prostacyclin pathway: prostacyclin analogs (intravenous epoprostenol; intravenous, subcutaneous, inhaled, or oral treprostinil; inhaled iloprost) and prostacyclin receptor agonist (selexipag). These vasodilators are only FDA approved for patients with Group 1 PAH based on their improvement in symptoms, 6-minute walk distance, WHO functional status, and hemodynamic measurements. More recently, a major RCT showed reduction in a composite outcome (death, hospitalization, progression, or unsatisfactory response) for combination therapy (using tadalafil and ambrisentan) compared to monotherapy. As a result, most patients with WHO/NYHA functional class II and III, should receive a combination of endothelin receptor antagonists and phosphodiesterase inhibitors as first-line therapy. For patients in WHO/NYHA functional class IV, a more aggressive approach is recommended with continuous prostacyclin infusion. Oral calcium channel blockers may be used in patients with a significant vasodilator response during cardiac catheterization. Anticoagulation was commonly used in the past but has fallen out of favor due to lack of efficacy.

Treatment of patients with Group 2 pulmonary hypertension (due to left heart failure) is discussed in Chapter 10. The main goal is to decrease pulmonary venous pressure by treating heart failure and volume overload, primarily with the use of diuretics.

Patients with Group 3 pulmonary hypertension (due to lung disease) should be assessed for hypoxemia at rest or with physical activity and, if present, should receive supplemental oxygen. Patients with COPD, interstitial lung disease, or obstructive sleep apnea should receive treatment for underlying disease. Inhaled treprostinil is the first therapy to be approved for patients with pulmonary hypertension due to interstitial lung disease since it improved exercise capacity based on 6-minute walk assessment.

For patients with Group 4 pulmonary hypertension (due to chronic thromboembolic disease), long-term anticoagulation is recommended. Additionally, patients with surgically accessible lesions and acceptable perioperative risk should undergo pulmonary thromboendarterectomy. For patients unable to undergo surgery or those with residual pulmonary hypertension postoperatively, medical therapy with riociguat or pulmonary artery balloon angioplasty should be considered.

Lung transplantation is a treatment option for selected patients with pulmonary hypertension when medical therapy is no longer effective. Double-lung transplant is the preferred method; in some cases, transplantation of the heart and both lungs is needed.

Prognosis

The prognosis of pulmonary hypertension varies by group. The prognosis of Group 1 patients has improved with the advent of pulmonary hypertension–specific therapy. Factors associated with poor prognosis include age older than 50 years, male sex, WHO/NYHA functional class III or IV, failure to improve to a lower functional class with therapy, and right ventricular dysfunction.

When to Refer

Patients in whom pulmonary hypertension is suspected or has been diagnosed should be referred early to a specialized pulmonary hypertension center for expert management.

When to Admit

- Patients with pulmonary hypertension, severe symptoms, and evidence of decompensated right heart failure with volume overload should be admitted to the hospital for aggressive diuresis.
- Patients with Group 1 pulmonary hypertension and functional class IV symptoms should be admitted to a specialized center for initiation of advanced therapies, such as intravenous prostacyclins.

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Sommer N et al. Current and future treatments of pulmonary arterial hypertension. Br J Pharmacol. 2021;178:6. [PMID: 32034759]
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PULMONARY VASCULITIS

Antineutrophil cytoplasmic autoantibody (ANCA)–associated vasculitides include granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis. All are associated with ANCA and similar features of glomerulonephritis.

Granulomatosis with polyangiitis is a small vessel vasculitis manifested in the upper and lower respiratory tracts. Chronic sinusitis, arthralgias, fever, skin rash, and weight loss are frequent presenting symptoms. Specific pulmonary complaints occur less often. The most common sign of lung disease is nodular pulmonary infiltrates, often with cavitation, seen on chest radiography. Tracheal stenosis and endobronchial disease are sometimes seen. The diagnosis is most often based on serologic testing and biopsy of lung, sinus tissue, or kidney with demonstration of necrotizing granulomatous vasculitis (Chapter 20).

Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) is an idiopathic multisystem vasculitis of small and medium-sized arteries that occurs in patients with asthma. The skin and lungs are most often involved, but other organs, including the paranasal sinuses, the heart, GI tract, liver, and peripheral nerves, may also be affected. Peripheral eosinophilia greater than 1500 cells/mcL (greater than 1.5×10^9/L) or greater than 10% of peripheral WBCs is the rule. Abnormalities on chest radiographs range from transient opacities to multiple nodules. This illness may be part of a spectrum that includes polyarteritis nodosa. The diagnosis requires demonstration of histologic features, including fibrinoid necrotizing epithelioid granulomas and eosinophilic granulomas.

Anti-glomerular basement membrane (anti-GBM) antibody disease (also called Goodpasture syndrome) is a small-vessel vasculitis resulting from circulating antibodies against an antigen component of the basement membrane of the glomerulus and alveoli. It is rare, seen in young adults, and has a slight male predominance. It causes diffuse alveolar hemorrhage, rapidly progressive glomerulonephritis, and kidney failure.

Treatment

Treatment of patients with pulmonary vasculitis requires immunosuppressive therapy. Combination therapy with corticosteroids and either rituximab or cyclophosphamide is recommended for induction. Then patients should be transitioned to maintenance therapy with rituximab, methotrexate, azathioprine, or mycophenolate. For anti-GBM antibody disease, the use of plasmapheresis during induction has been shown to improve outcomes.

Prognosis

Five-year survival rates in patients with these vasculitis syndromes have been improved by combination therapy. Complete remission can be achieved in over 90% of patients with granulomatosis with polyangiitis.

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ALVEOLAR HEMORRHAGE SYNDROMES

Diffuse alveolar hemorrhage may occur in a variety of immune and nonimmune disorders. Alveolar infiltrates on chest radiograph, dyspnea, anemia, hemoptysis and, occasionally, fever are characteristic. Rapid clearing of diffuse lung infiltrates within 2 days is a clue to the diagnosis of diffuse alveolar hemorrhage. Pulmonary hemorrhage can be associated with an increased DLCO, although this test is infrequently obtained. Sequential BAL on bronchoscopy is the preferred method for diagnosis with lavage aliquots becoming progressively more hemorrhagic.

Causes of diffuse **immune alveolar hemorrhage** include anti-basement membrane antibody disease (Goodpasture syndrome), granulomatosis with polyangiitis, systemic necrotizing vasculitis, pulmonary capillaritis associated with idiopathic rapidly progressive glomerulonephritis, SLE, and other vasculitic and collagen vascular diseases. **Nonimmune causes** of diffuse hemorrhage include coagulopathy, mitral stenosis, necrotizing pulmonary infection, drugs

(penicillamine), toxins (trimellitic anhydride), and idiopathic pulmonary hemosiderosis.

Idiopathic pulmonary hemosiderosis is a disease of children or young adults characterized by recurrent pulmonary hemorrhage; iron deficiency is typical. It is frequently associated with celiac disease. Treatment of acute episodes of hemorrhage with corticosteroids may be useful. Recurrent episodes of pulmonary hemorrhage may result in interstitial fibrosis and pulmonary failure.

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ENVIRONMENTAL & OCCUPATIONAL LUNG DISORDERS

SMOKE INHALATION

The inhalation of products of combustion may cause serious respiratory complications. As many as one-third of patients admitted to burn-treatment units have pulmonary injury from smoke inhalation. Morbidity and mortality due to smoke inhalation may exceed those attributed to the burns themselves. The death rate of patients with both severe burns and smoke inhalation exceeds 50%.

All patients in whom significant smoke inhalation is suspected must be assessed for three consequences of smoke inhalation: impaired tissue oxygenation, thermal injury to the upper airway, and injury to the lower airways and lung parenchyma. Impaired tissue oxygenation may result from inhalation of a hypoxic gas mixture, carbon monoxide or cyanide, or from alterations in $\dot{V}/\dot{Q}$ matching, and is an immediate threat to life. Immediate treatment with 100% oxygen is essential. The management of patients with carbon monoxide and cyanide poisoning is discussed in Chapter 38. The clinician must recognize that patients with carbon monoxide poisoning display a normal partial pressure of oxygen in arterial blood (Pao_2), but have a low *measured* (ie, not oximetric) hemoglobin saturation (Sao_2). Treatment with 100% oxygen should be continued until the measured carboxyhemoglobin level falls to less than 10% and concomitant metabolic acidosis has resolved.

Thermal injury to the mucosal surfaces of the upper airway occurs from inhalation of super-heated gases. Complications, including mucosal edema, upper airway obstruction, and impaired ability to clear oral secretions, usually become evident by 18–24 hours and produce inspiratory stridor. Respiratory failure occurs in severe cases. Early management (Chapter 37) includes the use of a high-humidity face mask with supplemental oxygen, gentle suctioning to evacuate oral secretions, elevation of the head 30 degrees to promote clearing of secretions, and topical epinephrine to reduce edema of the oropharyngeal mucous membrane. Helium-oxygen gas mixtures (Heliox) may reduce labored breathing due to critical upper airway narrowing. Close monitoring with ABGs and later with oximetry is important. Examination of the upper airway with a fiberoptic laryngoscope or bronchoscope is superior to routine physical examination. Endotracheal intubation is often necessary to maintain airway patency and is likely to be necessary in patients with deep facial burns or oropharyngeal or laryngeal edema. Tracheotomy should be avoided, if possible, because of an increased risk of pneumonia and death from sepsis.

Injury to the lower airways and lung parenchyma results from inhalation of toxic gases and products of combustion, including aldehydes and organic acids. The site of lung injury depends on the solubility of the gases inhaled, the duration of exposure, and the size of inhaled particles that transport noxious gases to distal lung units. Bronchorrhea and bronchospasm occur early after exposure along with dyspnea, tachypnea, and tachycardia. Labored breathing and cyanosis may follow. Physical examination at this stage reveals diffuse wheezing and rhonchi. Bronchiolar and alveolar edema (eg, ARDS) may develop within 1–2 days after exposure. Sloughing of the bronchiolar mucosa may occur within 2–3 days, leading to airway obstruction, atelectasis, and worsening hypoxemia. Bacterial colonization and pneumonia are common by 5–7 days after the exposure.

Treatment of smoke inhalation consists of supplemental oxygen, bronchodilators, suctioning of mucosal debris and mucopurulent secretions via an indwelling endotracheal tube, chest physical therapy to aid clearance of secretions, and adequate humidification of inspired gases. Positive end-expiratory pressure (PEEP) has been advocated to treat bronchiolar edema. Judicious fluid management and close monitoring for secondary bacterial infection round out the management protocol.

The routine use of corticosteroids for lung injury from smoke inhalation has been shown to be ineffective and may even be harmful. Routine or prophylactic use of antibiotics is not recommended.

Patients who survive should be watched for the late development of bronchiolitis obliterans.

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E-CIGARETTE- OR VAPING PRODUCT–ASSOCIATED LUNG INJURY

General Considerations

An outbreak of e-cigarette- or vaping product–associated lung injury (EVALI) began in the United States in 2019. Approximately 66% of patients have been male and 80% are under age 35. Over 95% of reported cases required hospitalization: 47% were admitted to intensive care, 22% were intubated, and many died. Based on the characteristics of these patients, the diagnosis of EVALI requires reported use of e-cigarette or vaping products within 3 months of symptom onset, compatible chest imaging findings, and an evaluation that excludes infectious etiologies.

No single causative agent has been identified. Most cases involved vaping products containing tetrahydrocannabinol (THC) or nicotine or both. Postulated factors contributing to the development of EVALI include e-cigarette flavorings, exposure to diacetyl (a popcorn flavoring that has been associated with lung injury), THC, adulteration of THC, adulteration of delivery devices, and vitamin E acetate (used as a thickening agent).

Clinical Findings

A. Symptoms and Signs

Patients with EVALI have respiratory symptoms (95%), including cough, shortness of breath, and chest pain; GI symptoms (77%), including nausea, vomiting, and diarrhea; and constitutional symptoms (85%), including fever, chills, and weight loss. The illness is usually acute to subacute with patients having symptoms for days to weeks before seeking health care.

Tachycardia and tachypnea are present in 55% and 45% of patients, respectively. Of note, 57% of cases have a recorded room air oxygen saturation of less than 95%. Given the nonspecific nature of the presentation especially during influenza season and the COVID-19 pandemic, providers must have a high degree of clinical suspicion and ask patients specifically about vaping.

B. Laboratory Findings

There are no laboratory findings specific for the diagnosis of EVALI. There may be leukocytosis, elevated CRP, and elevated ESR.

C. Imaging

Case series of chest imaging findings in EVALI show various patterns of lung injury. Chest radiographs typically show bilateral pulmonary opacities. Chest CT scans are nonspecific and may show patterns seen in other disorders, such as hypersensitivity pneumonitis, ARDS, diffuse alveolar hemorrhage, acute eosinophilic pneumonia, lipoid pneumonia, giant cell interstitial pneumonia, and organizing pneumonia.

Differential Diagnosis

The EVALI case definition requires a negative work-up for infectious causes. Other diagnoses to consider include acute eosinophilic pneumonia, ARDS, hypersensitivity pneumonitis, lipoid pneumonia, and organizing pneumonia. Influenza testing should be done in season, and SARS-CoV-2 testing, as indicated.

Treatment

In published reports of hospitalized patients with EVALI who have received corticosteroids, rapid improvement has been described. Symptoms of fatigue, dyspnea, decreased exercise capacity, and cough may persist for months.

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Traboulsi H et al. Inhalation toxicology of vaping products and implications for pulmonary health. Int J Mol Sci. 2020;21:3495. [PMID: 32429092]

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PULMONARY ASPIRATION SYNDROMES

1. Acute Aspiration of Gastric Contents (Mendelson Syndrome)

Acute aspiration of gastric contents may be catastrophic. The pulmonary response depends on the characteristics and amount of gastric contents aspirated. The more acidic the material, the greater the degree of chemical pneumonitis. Aspiration of pure gastric acid (pH < 2.5) causes extensive desquamation of the bronchial epithelium, bronchiolitis, hemorrhage, and pulmonary edema. Acute gastric aspiration is one of the most common causes of ARDS. The clinical picture is one of abrupt onset of respiratory distress, with cough, wheezing, fever, and tachypnea. Crackles may be audible at the bases of the lungs. Hypoxemia may be noted immediately after aspiration occurs. Radiographic abnormalities, consisting of patchy alveolar opacities in dependent lung zones, appear within a few hours. If particulate food matter has been aspirated along with gastric acid, radiographic features of bronchial obstruction may be observed. Fever and leukocytosis are common even in the absence of infection.

Treatment of acute aspiration of gastric contents consists of supplemental oxygen, measures to maintain the airway, and the usual measures for treatment of acute respiratory failure. There is no evidence to support the routine use of prophylactic antibiotics or corticosteroids. Secondary pulmonary infection, which occurs in about one-fourth of patients, typically appears 2–3 days after aspiration. Management of infection depends on the observed flora from the tracheobronchial tree. Hypotension or shock secondary to alveolar capillary membrane injury and intravascular volume depletion is common and is managed with the judicious administration of intravenous fluids or vasopressors or both.

2. Chronic Aspiration of Gastric Contents

Chronic aspiration of gastric contents may result from primary disorders of the larynx or the esophagus, such as achalasia, esophageal stricture, systemic sclerosis (scleroderma), esophageal carcinoma, esophagitis, and GERD. In GERD, relaxation of the tone of the lower esophageal sphincter allows reflux of gastric contents into the esophagus and predisposes to chronic pulmonary aspiration, especially when supine. Cigarette smoking, consumption

of alcohol or caffeine, and theophylline use are all known to relax the lower esophageal sphincter. Pulmonary disorders linked to GERD and chronic aspiration include asthma, chronic cough, bronchiectasis, and pulmonary fibrosis. Even in the absence of aspiration, acid in the esophagus may trigger bronchospasm or bronchial hyperreactivity through reflex mechanisms.

The diagnosis and management of GERD and chronic aspiration are challenging. A discussion of strategies for the evaluation, prevention, and management of extraesophageal reflux manifestations can be found in Chapter 15.

3. "Café Coronary"

Acute obstruction of the upper airway by food is associated with difficulty swallowing, old age, dental problems that impair chewing, and use of alcohol and sedative drugs. The Heimlich procedure is lifesaving in many cases.

4. Retention of an Aspirated Foreign Body

Retention of an aspirated foreign body in the tracheobronchial tree may produce both acute and chronic conditions, including atelectasis, postobstructive hyperinflation, both acute and recurrent pneumonia, bronchiectasis, and lung abscess. Occasionally, a misdiagnosis of asthma, COPD, or lung cancer is made in adult patients who have aspirated a foreign body. The plain chest radiograph usually suggests the site of the foreign body. In some cases, an expiratory film, demonstrating regional hyperinflation due to a check-valve effect, is helpful. Bronchoscopy is usually necessary to establish the diagnosis and attempt removal of the foreign body.

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OCCUPATIONAL PULMONARY DISEASES

Many acute and chronic pulmonary diseases are directly related to inhalation of noxious substances encountered in the workplace. Disorders that are linked to occupational exposures may be classified as follows: (1) pneumoconioses, (2) hypersensitivity pneumonitis, (3) obstructive airway disorders, (4) toxic lung injury, (5) lung cancer, (6) pleural diseases, and (7) other occupational pulmonary diseases.

1. Pneumoconioses

Pneumoconioses are chronic fibrotic lung diseases caused by the inhalation of inert inorganic dusts. Pneumoconioses range from asymptomatic disorders with diffuse nodular opacities on chest radiograph to severe, symptomatic, life-shortening disorders. Clinically important pneumoconioses include coal worker's pneumoconiosis, silicosis, and asbestosis (Table 9–20). Treatment for each is supportive; pulmonary rehabilitation may be considered.

A. Coal Worker's Pneumoconiosis

In coal worker's pneumoconiosis, ingestion of inhaled coal dust by alveolar macrophages leads to the formation of coal macules, usually 2–5 mm in diameter, that appear on chest radiograph as diffuse small opacities that are especially prominent in the upper lung. Simple coal worker's pneumoconiosis is usually asymptomatic; abnormalities of PFTs are unimpressive. In complicated coal worker's pneumoconiosis **("progressive massive fibrosis"),** conglomeration and contraction in the upper lung zones occur, with radiographic features resembling complicated silicosis. **Caplan syndrome** is a rare condition characterized by the presence of necrobiotic rheumatoid nodules (1–5 cm in diameter) in the periphery of the lung in coal workers with rheumatoid arthritis.

B. Silicosis

In silicosis, extensive or prolonged inhalation of free silica (silicon dioxide) particles (sandblasters, foundry, granite

Table 9–20. Selected pneumoconioses.

Disease	Agent	Occupations
Asbestosis	Asbestos	Mining, insulation, construction, shipbuilding
Baritosis	Barium salts	Glass and insecticide manufacturing
Coal worker's pneumoconiosis	Coal dust	Coal mining
Kaolin pneumoconiosis	Sand, mica, aluminum silicate	Mining of china clay; pottery and cement work
Shaver disease	Aluminum powder	Manufacture of corundum
Siderosis	Metallic iron or iron oxide	Mining, welding, foundry work
Silicosis	Free silica (silicon dioxide)	Rock mining, quarrying, stone cutting, tunneling, sandblasting, pottery, diatomaceous earth
Stannosis	Tin, tin oxide	Mining, tin-working, smelting
Talcosis	Magnesium silicate	Mining, insulation, construction, shipbuilding

and stone cutting, molding, ceramics) in the respirable range (0.3–5 mcm) causes the formation of small rounded opacities (silicotic nodules) throughout the lung. Calcification of the periphery of hilar lymph nodes ("eggshell" calcification) is an unusual radiographic finding that strongly suggests silicosis. Simple silicosis is usually asymptomatic and has no effect on routine PFTs; in complicated silicosis, large conglomerate densities appear in the upper lung and are accompanied by dyspnea and obstructive and restrictive pulmonary dysfunction. The incidence of pulmonary tuberculosis is increased in patients with silicosis. All patients with silicosis should have a tuberculin skin test and a chest radiograph to rule out tuberculosis.

C. Asbestosis

Asbestosis is a nodular interstitial fibrosis occurring in workers exposed to asbestos fibers (shipyard and construction workers, pipe fitters, insulators) over many years (typically 10–20 years). Patients with asbestosis usually first seek medical attention at least 15 years after exposure with the following symptoms and signs: progressive dyspnea, inspiratory crackles, and in some cases, clubbing and cyanosis. The radiographic features of asbestosis include linear streaking at the lung bases, opacities of various shapes and sizes, and honeycomb changes in advanced cases. The presence of pleural calcifications may be a clue to diagnosis. High-resolution CT scanning is the best imaging method for asbestosis because of its ability to detect parenchymal fibrosis and define the presence of coexisting pleural plaques. Cigarette smoking in asbestos workers increases the prevalence of radiographic pleural and parenchymal changes and markedly increases the incidence of lung carcinoma. It may also interfere with the clearance of short asbestos fibers from the lung. PFTs show restrictive dysfunction and reduced diffusing capacity. There is no specific treatment.

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2. Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (also called extrinsic allergic alveolitis) is a nonatopic, nonasthmatic inflammatory pulmonary disease. It is manifested mainly as an occupational disease (Table 9–21), in which exposure to inhaled organic antigens leads to an acute illness. Prompt diagnosis is essential since symptoms are usually reversible if the offending antigen is removed from the patient's environment early in the course of illness. Continued exposure may lead to progressive disease. The histopathology of acute hypersensitivity pneumonitis is characterized by interstitial infiltrates of lymphocytes and plasma cells, with noncaseating granulomas in the interstitium and air spaces.

Table 9–21. Selected causes of hypersensitivity pneumonitis.

Disease	Antigen	Source
Farmer's lung	*Saccharopolyspora rectivirgula* (formerly, *Micropolyspora faeni*), *Thermoactinomyces vulgaris*	Moldy hay
"Humidifier" lung	Thermophilic actinomycetes	Contaminated humidifiers, heating systems, or air conditioners
Bird fancier's lung	Avian proteins	Bird serum and excreta
Bagassosis	*Thermoactinomyces sacchari* and *T vulgaris*	Moldy sugar cane fiber (bagasse)
Sequoiosis	*Graphium, Aureobasidium,* and other fungi	Moldy redwood sawdust
Maple bark stripper's disease	*Cryptostroma (Coniosporium) corticale*	Rotting maple tree logs or bark
Mushroom picker's disease	Same as farmer's lung	Moldy compost
Suberosis	*Penicillium frequentans*	Moldy cork dust
Detergent worker's lung	*Bacillus subtilis* enzyme	Enzyme additives

Clinical Findings

A. Acute Illness

The symptoms are characterized by sudden onset of malaise, chills, fever, cough, dyspnea, and nausea 4–8 hours after exposure to the offending antigen. Bibasilar crackles, tachypnea, tachycardia, and (occasionally) cyanosis are noted. Small nodular densities sparing the apices and bases of the lungs are noted on chest radiograph. Laboratory studies reveal an increase in the WBC count with a shift to the left, hypoxemia, and the presence of precipitating antibodies to the offending agent in serum. Hypersensitivity pneumonitis antibody panels against common offending antigens are available; positive results, while supportive, do not establish a definitive diagnosis. PFTs reveal restrictive dysfunction and reduced diffusing capacity.

B. Subacute and Chronic Illness

A subacute hypersensitivity pneumonitis syndrome (15% of cases) is characterized by the insidious onset of chronic cough and slowly progressive dyspnea, anorexia, and weight loss. Chronic exposure leads to progressive respiratory insufficiency and the appearance of pulmonary

fibrosis on chest imaging. Surgical lung biopsy may be necessary for the diagnosis of subacute and chronic hypersensitivity pneumonitis. Even with surgical lung biopsy, however, chronic hypersensitivity pneumonitis may be difficult to diagnose because histopathologic patterns overlap with several idiopathic interstitial pneumonias.

Treatment

Treatment of acute hypersensitivity pneumonitis consists of identification of the offending agent and avoidance of further exposure. In severe acute or protracted cases, oral corticosteroids (prednisone, 0.5 mg/kg daily as a single morning dose for 2 weeks, tapered to nil over 4–6 weeks) may be given. Change in occupation is often unavoidable.

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Nogueira R et al. Hypersensitivity pneumonitis: antigen diversity and disease implications. Pulmonology. 2019;25:97. [PMID: 30126802]

3. Other Occupational Pulmonary Diseases

Occupational diseases of the pleura may result from exposure to asbestos or talc. Inhalation of talc causes pleural plaques that are like those caused by asbestos. Benign asbestos pleural effusion occurs in some asbestos workers and may cause chronic blunting of the costophrenic angle on chest radiograph.

Occupational agents are also responsible for other pulmonary disorders, with a range of pathologies including occupational asthma, occupational COPD, interstitial lung diseases, and lung cancer. For this reason, it is important to obtain a thorough occupational history in any patient presenting with pulmonary symptoms.

Specific examples of inorganic agents associated with interstitial lung disease include anthracite coal dust (coal workers' pneumoconiosis), crystalline and nonfibrous silicates (silicosis), asbestos (asbestosis, pleural plaques, benign pleural effusion, adenoma, malignant mesothelioma), beryllium (berylliosis, which is very similar to sarcoidosis), and cobalt (hard metal lung disease). Organic dust from farm work, animal or bird exposure, or vegetable stores may cause extrinsic allergic alveolitis or hypersensitivity pneumonitis.

Unusual outbreaks (including "popcorn-worker's lung" and other diacetyl flavoring exposure causing bronchiolitis obliterans, "flock worker's lung" following synthetic fiber exposure) are occasionally reported.

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MEDICATION-INDUCED LUNG DISEASE

Typical patterns of pulmonary response to medications implicated in medication-induced respiratory disease are summarized in Table 9–22. Pulmonary injury due to medications occurs because of allergic reactions, idiosyncratic reactions, overdose, or undesirable side effects. In most patients, the mechanism of pulmonary injury is unknown.

Precise diagnosis of medication-induced pulmonary disease is often difficult because results of routine laboratory studies are not helpful and radiographic findings are not specific. A high index of suspicion and a thorough history of medication usage are critical to establishing the diagnosis of medication-induced lung disease. The clinical response to cessation of the suspected offending agent is also helpful. Acute episodes of medication-induced pulmonary disease may disappear 24–48 hours after the medication has been discontinued, but chronic syndromes may

Table 9–22. Pulmonary manifestations of selected medication toxicities.

Asthma	**Pulmonary edema**
Beta-blockers	Noncardiogenic
Aspirin	Aspirin
NSAIDs	Chlordiazepoxide
Histamine	Cocaine
Methacholine	Ethchlorvynol
Acetylcysteine	Heroin/opiates
Aerosolized pentamidine	Cardiogenic
Any nebulized medication	Beta-blockers
Chronic cough	**Pleural effusion**
ACE inhibitors	Bromocriptine
Pulmonary infiltration	Nitrofurantoin
Without eosinophilia	Any drug inducing SLE
Amitriptyline	Methysergide
Azathioprine	Chemotherapeutic agents (eg, carmustine, cyclophosphamide, dasatinib, docetaxel, GM-CSF, methotrexate)
Amiodarone	Tyrosine kinase inhibitors
With eosinophilia	**Mediastinal widening**
Sulfonamides	Phenytoin
L-Tryptophan	Corticosteroids
Nitrofurantoin	Methotrexate
Penicillin	**Respiratory failure**
Methotrexate	Neuromuscular blockade
Crack cocaine	Aminoglycosides
Drug-induced SLE	Paralytic agents
Hydralazine	**CNS depression**
Procainamide	Sedatives
Isoniazid	Hypnotics
Chlorpromazine	Opioids
Phenytoin	Alcohol
Interstitial pneumonitis/fibrosis	Tricyclic antidepressants
Nitrofurantoin	
Bleomycin	
Busulfan	
Cyclophosphamide	
Immune checkpoint inhibitors	
Methysergide	
Phenytoin	

GM-CSF, granulocyte-macrophage colony-stimulating factor.

take longer to resolve. Challenge tests to confirm the diagnosis are risky and rarely performed.

Treatment of medication-induced lung disease consists of discontinuing the offending agent immediately, managing the pulmonary symptoms appropriately, and treating with corticosteroids if pulmonary toxicity is rapidly progressive. Randomized data supporting the use of corticosteroids in medication-associated pneumonitis is lacking, but observational data supports use in severe cases. Immune checkpoint inhibitors, now commonly used treatments for a variety of malignant and nonmalignant conditions, are associated with at least a 5% risk of pneumonitis, which carries mortality of up to 20% when severe. Observational data support concurrent corticosteroid treatment in these cases.

Inhalation of crack cocaine may cause a spectrum of acute pulmonary syndromes, including pulmonary infiltration with eosinophilia, pneumothorax and pneumomediastinum, bronchiolitis obliterans, and acute respiratory failure associated with diffuse alveolar damage and alveolar hemorrhage. Corticosteroids have been used with variable success to treat alveolar hemorrhage.

Long K et al. Pulmonary toxicity of systemic lung cancer therapy. Respirology. 2020;25:72. [PMID: 32729207]
Suresh K. Immune checkpoint immunotherapy for non-small cell lung cancer: benefits and pulmonary toxicities. Chest. 2018;154:1416. [PMID: 301891190]

RADIATION LUNG INJURY

The lung is an exquisitely radiosensitive organ that can be damaged by external beam radiation therapy. The degree of pulmonary injury is determined by the volume of lung irradiated, the dose and rate of exposure, and potentiating factors (eg, concurrent chemotherapy, previous radiation therapy in the same area, and simultaneous withdrawal of corticosteroid therapy). Symptomatic radiation lung injury occurs in about 10% of patients treated for carcinoma of the breast, 5–15% of patients treated for carcinoma of the lung, and 5–35% of patients treated for lymphoma. Two phases of the pulmonary response to radiation are apparent: an acute phase (radiation pneumonitis) and a chronic phase (radiation fibrosis).

1. Radiation Pneumonitis

Acute radiation pneumonitis usually occurs 2–3 months (range 1–6 months) after completion of radiotherapy and is characterized by insidious onset of dyspnea, intractable dry cough, chest fullness or pain, weakness, and fever. Late radiation pneumonitis may develop 6–12 months after completion of radiation. Occasionally, patients who are months to years removed from radiation therapy will experience "radiation recall" with an inflammatory reaction in the radiated region after treatment with a new round of chemotherapy; this phenomenon has also been reported with immune checkpoint inhibitors. The dominant histopathologic findings are a lymphocytic interstitial pneumonitis progressing to an exudative alveolitis. Inspiratory crackles may be heard in the involved area. In severe disease, respiratory distress and cyanosis occur that are characteristic of ARDS. An increased WBC count and elevated ESR are common. PFTs reveal reduced lung volumes, reduced lung compliance, hypoxemia, reduced diffusing capacity, and reduced maximum voluntary ventilation. Chest radiography, which correlates poorly with the presence of symptoms, usually demonstrates alveolar or nodular opacities limited to the irradiated area. Air bronchograms are often observed. Sharp borders of an opacity may help distinguish radiation pneumonitis from other conditions, such as infectious pneumonia, lymphangitic spread of carcinoma, and recurrent tumor; however, the opacity may extend beyond the radiation field.

No specific therapy is proved to be effective in radiation pneumonitis, but prednisone (1 mg/kg/day orally) is commonly given immediately for about 1 week; higher doses may be given in patients who are critically ill. The dose is reduced and maintained at 20–40 mg/day for several weeks, then slowly tapered. Radiation pneumonitis may improve in 2–3 weeks following onset of symptoms as the exudative phase resolves. Acute respiratory failure, if present, is treated supportively. Death from ARDS is unusual in radiation pneumonitis.

Giuranno L et al. Radiation-induced lung injury (RILI). Front Oncol. 2019;9:877. [PMID: 31555602]
Hanania AN et al. Radiation-induced lung injury: assessment and management. Chest. 2019;156:150. [PMID: 30998908]
Kasmann L et al. Radiation-induced lung toxicity—cellular and molecular mechanisms of pathogenesis, management, and literature review. Radiat Oncol. 2020;15:214. [PMID: 32912295]
Lu L et al. Radiation-induced lung injury: latest molecular developments, therapeutic approaches, and clinical guidance. Clin Exp Med. 2019;19:417. [PMID: 31313081]
Teng F et al. Radiation recall pneumonitis induced by PD-1/PD-L1 blockades: mechanisms and therapeutic implications. BMC Med. 2020;18:275. [PMID: 32943072]

2. Pulmonary Radiation Fibrosis

Radiation fibrosis may occur with or without antecedent radiation pneumonitis. Radiographic findings include obliteration of normal lung markings, dense interstitial and pleural fibrosis, reduced lung volumes, tenting of the diaphragm, and sharp delineation of the irradiated area. No specific therapy is proven effective, and corticosteroids have no value. Pulmonary fibrosis may develop after an intervening period (6–12 months) of well-being in patients who experience radiation pneumonitis. Pulmonary radiation fibrosis occurs in most patients who receive a full course of radiation therapy for cancer of the lung or breast. Most patients are asymptomatic, although slowly progressive dyspnea may occur.

Giuranno L et al. Radiation-induced lung injury (RILI). Front Oncol. 2019;9:877. [PMID: 31555602]

PLEURAL DISEASES

PLEURITIS

Pleuritic pain due to inflammation of the parietal pleura is generally localized, sharp, and fleeting; it is made worse by coughing, sneezing, deep breathing, or movement.

When the central portion of the diaphragmatic parietal pleura is irritated, pain may be referred to the ipsilateral shoulder. There are numerous causes of pleuritis. The setting in which pleuritic pain develops helps narrow the differential diagnosis. In young, otherwise healthy individuals, pleuritis is usually caused by viral respiratory infections or pneumonia (including tuberculosis in endemic regions), while PE, inflammatory disorders (serositis), malignancy, and drug reactions may also be considered in the proper context. The presence of pleural effusion, pleural thickening, or air in the pleural space requires further diagnostic and therapeutic measures.

Treatment of pleuritis consists of treating the underlying condition. Anti-inflammatory analgesic medications are often helpful for pain relief. Opioids may be used if NSAIDs are ineffective or are contraindicated, provided retention of airway secretions is not a concern.

Shaw JA et al. Pleural tuberculosis: a concise clinical review. Clin Respir J. 2018;12:1779. [PMID: 29660258]

PLEURAL EFFUSION

ESSENTIALS OF DIAGNOSIS

- May be asymptomatic; chest pain frequently seen in the setting of pleuritis, trauma, or infection; dyspnea is common with large effusions.
- Dullness to percussion and decreased breath sounds over the effusion.
- Radiographic evidence of pleural effusion.
- Diagnostic findings on thoracentesis.

General Considerations

There is constant movement of fluid from parietal pleural capillaries into the pleural space at a rate of 0.01 mL/kg body weight/h. Absorption of pleural fluid occurs through parietal pleural lymphatics. The resultant homeostasis leaves 5–15 mL of fluid in the normal pleural space. A pleural effusion is an abnormal accumulation of fluid in the pleural space. Pleural effusions may be classified by differential diagnosis (Table 9–23) or by underlying pathophysiology. Five pathophysiologic processes account for most pleural effusions: increased production of fluid in the setting of normal capillaries due to increased hydrostatic or decreased oncotic pressures **(transudates);** increased production of fluid due to abnormal capillary permeability **(exudates);** decreased lymphatic clearance of fluid from the pleural space **(exudates);** infection in the pleural space **(empyema);** and bleeding into the pleural space **(hemothorax).**

Diagnostic thoracentesis should be performed whenever there is a new pleural effusion and no clinically apparent cause. Observation is appropriate in some situations (eg, symmetric bilateral pleural effusions in the setting of heart failure), but an atypical presentation or failure of an effusion to resolve as expected warrants thoracentesis to identify the underlying process.

Table 9–23. Causes of pleural fluid transudates and exudates.

Transudates	Exudates
Heart failure	Pneumonia (parapneumonic effusion, including empyema)
Cirrhosis with ascites	Cancer
Nephrotic syndrome	PE
Peritoneal dialysis	Bacterial infection (including empyema)
Myxedema	Tuberculosis
Atelectasis (acute)	Connective tissue disease
Constrictive pericarditis	Viral infection
Superior vena cava obstruction	Fungal infection
PE	Rickettsial infection
	Parasitic infection
	Asbestos
	Meigs syndrome
	Pancreatic disease
	Uremia
	Chronic atelectasis
	Trapped lung
	Chylothorax
	Sarcoidosis
	Drug reaction
	Post–myocardial injury syndrome

Clinical Findings

A. Symptoms and Signs

Patients with pleural effusions most often report dyspnea, cough, or respirophasic chest pain. Symptoms are more common in patients with existing cardiopulmonary disease. Small pleural effusions are less likely to be symptomatic than larger effusions. Physical findings are usually absent in small effusions. Larger effusions may present with dullness to percussion and diminished or absent breath sounds over the effusion. Compressive atelectasis may cause bronchial breath sounds and egophony just above the effusion. A massive effusion with increased intrapleural pressure may cause contralateral shift of the trachea and bulging of the intercostal spaces. A pleural friction rub indicates pulmonary infarction or pleuritis.

B. Laboratory Findings

The gross appearance of pleural fluid helps identify several types of pleural effusion. Grossly purulent fluid signifies empyema. Milky white pleural fluid should be centrifuged. A clear supernatant above a pellet of white cells indicates empyema, whereas a persistently turbid supernatant suggests a **chylous effusion;** analysis of this supernatant reveals chylomicrons and a high triglyceride level (greater than 100 mg/dL [1 mmol/L]), often from disruption of the thoracic duct. **Hemorrhagic pleural effusion** is a mixture of blood and pleural fluid. Ten thousand red cells per

microliter create blood-tinged pleural fluid; 100,000 red cells/mcL (100×10^9/L) create grossly bloody pleural fluid. **Hemothorax** is the presence of gross blood in the pleural space, usually following chest trauma or instrumentation. It is defined as a ratio of pleural fluid hematocrit to peripheral blood hematocrit greater than 0.5.

Pleural fluid samples should be sent for measurement of protein, glucose, and LD in addition to total and differential WBC counts. Chemistry determinations are used to classify effusions as transudates or exudates. This classification is important because the differential diagnosis and subsequent evaluation for each entity varies (Table 9–23). A **pleural exudate** is an effusion that has one or more of the following laboratory features: (1) ratio of pleural fluid protein to serum protein greater than 0.5; (2) ratio of pleural fluid LD to serum LD greater than 0.6; (3) pleural fluid LD greater than two-thirds the upper limit of normal serum LD. Alternative diagnostic criteria that do not require the simultaneous sampling of serum but that perform similarly include the "two-test" (pleural fluid cholesterol greater than 45 mg/dL, pleural fluid LD greater than 0.45 times upper limit of normal serum LD) and the "three-test" (which adds pleural fluid protein greater than 2.9 g/dL). **Pleural transudates** occur in the setting of normal capillary integrity and demonstrate none of the laboratory features of exudates. A transudate suggests the absence of local pleural disease; characteristic laboratory findings include a glucose near to serum glucose, pH between 7.40 and 7.55 (if properly measured), and fewer than 1000 WBCs/mcL (1.0×10^9/L) with a predominance of mononuclear cells. It is worthwhile to note that discrimination of exudate from transudate is less reliable near the cutoff values for any of the criteria, and that effective diuresis may increase the protein or LD concentration in the pleural fluid as water is reabsorbed, thus creating a borderline "pseudoexudative" chemistry in transudative states such as heart failure.

Heart failure accounts for most transudates. Bacterial pneumonia, cancer, and tuberculosis (in endemic regions) are the most common causes of exudative effusion. Other causes of exudates with characteristic laboratory findings are summarized in Table 9–24.

Table 9–24. Characteristics of important exudative pleural effusions.

Etiology or Type of Effusion	Gross Appearance	WBC Count (cells/mcL)	RBC Count (cells/mcL)	Glucose	Comments
Malignancy	Turbid to bloody; occasionally serous	1000–100,000 ($1.0–100 \times 10^9$/L) M	100 (0.1×10^9/L) to several hundred thousand	Equal to serum levels; < 60 mg/dL in 15% of cases	Eosinophilia uncommon; positive results on cytologic examination
Uncomplicated parapneumonic	Clear to turbid	5000–25,000 ($5.0–25 \times 10^9$/L) P	< 5000 (5.0×10^9/L)	Equal to serum levels	Tube thoracostomy unnecessary
Empyema	Turbid to purulent	25,000–100,000 ($25–100 \times 10^9$/L) P	< 5000 (5.0×10^9/L)	Less than serum levels; often very low	Drainage necessary; putrid odor suggests anaerobic infection
Tuberculosis	Serous to serosanguineous	5000–10,000 ($5.0–10 \times 10^9$/L) M	< 10,000 (10×10^9/L)	Equal to serum levels; occasionally < 60 mg/dL	Protein > 4.0 g/dL (may exceed 5 g/dL); frequently lymphocyte predominant (> 50%); eosinophils (> 10%) or mesothelial cells (> 5%) make diagnosis unlikely; see text for additional diagnostic tests
Rheumatoid	Turbid; greenish yellow	1000–20,000 ($1.0–20 \times 10^9$/L) M or P	< 1000 (1.0×10^9/L)	< 40 mg/dL	Secondary empyema common; high LD, low complement, high rheumatoid factor, cholesterol crystals are characteristic
Pulmonary infarction	Serous to grossly bloody	1000–50,000 ($1.0–50 \times 10^9$/L) M or P	100 (0.1×10^9/L) to > 100,000 (100×10^9/L)	Equal to serum levels	Variable findings; no pathognomonic features
Esophageal rupture	Turbid to purulent; red-brown	< 5000 (5.0×10^9/L) to > 50,000 (50×10^9/L) P	1000–10,000 ($1.0–10 \times 10^9$/L)	Usually low	High amylase level (salivary origin); pneumothorax in 25% of cases; effusion usually on left side; pH < 6.0 strongly suggests diagnosis
Pancreatitis	Turbid to serosanguineous	1000–50,000 ($1.0–50 \times 10^9$/L) P	1000–10,000 ($1.0–10 \times 10^9$/L)	Equal to serum levels	Usually left-sided; high amylase level

M, mononuclear cell predominance; P, polymorphonuclear leukocyte predominance.

Pleural fluid pH (normal = 7.60) is useful in the assessment of parapneumonic effusions, if it can be reliably measured, and is more useful than glucose measurement in determining need for drainage. A pH less than 7.20 suggests the need for drainage of the pleural space. An elevated amylase level in pleural fluid suggests pancreatitis, pancreatic pseudocyst, adenocarcinoma of the lung or pancreas, or esophageal rupture.

Suspected tuberculous pleural effusion should be evaluated by thoracentesis with culture, although pleural fluid culture positivity for *M tuberculosis* is low. Tests for pleural fluid adenosine deaminase (approximately 90% sensitivity and specificity for pleural tuberculosis at levels greater than 60 U/L, tuberculosis rare if level is less than 40 U/L) and interferon-gamma (89% sensitivity, 97% specificity in a meta-analysis) can be helpful diagnostic aids, particularly in making decisions to pursue invasive testing in complex patients. Closed pleural biopsy is more sensitive than pleural fluid culture for diagnosis, revealing granulomatous inflammation in approximately 60% of patients, and culture of three pleural biopsy specimens combined with histologic examination of a pleural biopsy for granulomas yields a diagnosis in up to 90% of patients.

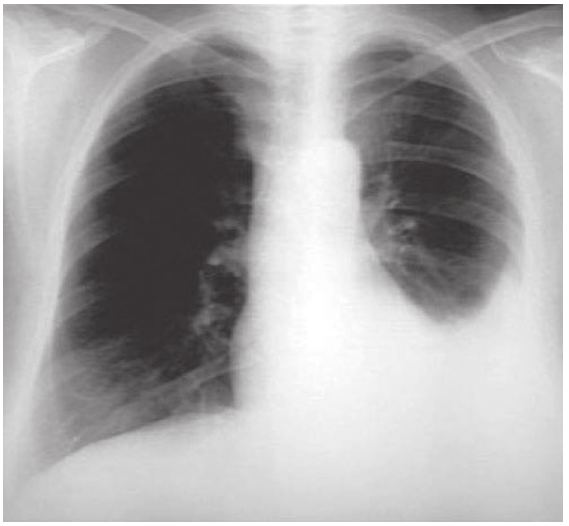
Between 40% and 80% of exudative pleural effusions are malignant, while over 90% of malignant pleural effusions are exudative. Almost any form of cancer may cause effusions, but the most common causes are lung cancer (one-third of cases) and breast cancer. In 5–10% of malignant pleural effusions, no primary tumor is identified.

Pleural fluid specimens should be sent for cytologic examination in all cases of exudative effusions in patients suspected of harboring an underlying malignancy. The diagnostic yield depends on the nature and extent of the underlying malignancy. Sensitivity is between 50% and 65% and increases with serial sampling. In a patient with a high prior probability of malignancy, a negative cytologic examination should be followed by one repeat thoracentesis. If that examination is negative, thoracoscopy is preferred to closed pleural biopsy. The sensitivity of thoracoscopy is 92–96%.

The term **paramalignant** pleural effusion refers to an effusion in a patient with cancer when repeated attempts to identify tumor cells in the pleura or pleural fluid are nondiagnostic but when there is a presumptive relation to the underlying malignancy. For example, superior vena cava syndrome with elevated systemic venous pressures causing a transudative effusion would be "paramalignant."

C. Imaging

The lung is less dense than water and floats on pleural fluid that accumulates in dependent regions. Subpulmonic fluid may appear as lateral displacement of the apex of the diaphragm with an abrupt slope to the costophrenic sulcus or a greater than 2-cm separation between the gastric air bubble and the lung. On a standard upright chest radiograph (Figure 9–7), approximately 75–100 mL of pleural fluid must accumulate in the posterior costophrenic sulcus to be visible on the lateral view, and 175–200 mL must be present in the lateral costophrenic sulcus to be visible on the frontal view. Chest CT scans may identify as little as 10 mL of fluid. At least 1 cm of fluid on the decubitus view is necessary to permit blind thoracentesis. Ultrasonography increases the safety of thoracentesis and should be incorporated routinely by trained users.



▲ **Figure 9–7. Left pleural effusion. Frontal chest radiograph showing a meniscus-shaped density at the left costophrenic angle sulcus indicative of a moderate-sized pleural effusion.** (Reproduced, with permission, from Lechner AJ, Matuschak GM, Brink DS. *Respiratory: An Integrated Approach to Disease*. McGraw-Hill, 2012.)

Pleural fluid may become trapped (loculated) by pleural adhesions, thereby forming unusual collections along the lateral chest wall or within lung fissures. Round or oval fluid collections in fissures that resemble intraparenchymal masses are called pseudotumors.

Treatment

A. Transudative Pleural Effusion

Transudative pleural effusions characteristically occur in the absence of pleural disease. Therefore, treatment is directed at the underlying condition. Therapeutic thoracentesis for severe dyspnea typically offers only transient benefit. Pleurodesis or indwelling pleural catheters are rarely indicated but are appropriate for management of symptoms in selected patients whose symptoms respond to drainage and whose effusions are refractory to maximal medical therapy.

B. Malignant Pleural Effusion

Chemotherapy, radiation therapy, or both offer temporary control in some malignant effusions but are generally ineffective in lung cancer in the pleural space except for small-cell lung cancer. Asymptomatic malignant effusions usually do not require specific treatment. Symptomatic patients should be offered pleural drainage, either via initial therapeutic thoracentesis to determine symptomatic response to drainage, following which an indwelling pleural catheter can be placed, or via immediate placement of an indwelling

pleural catheter. Indwelling pleural catheter placement is associated with shorter hospital stays than pleurodesis. Indwelling pleural catheters often effect a pleurodesis over time, at which point the catheter can be removed.

C. Parapneumonic Pleural Effusion

Parapneumonic pleural effusions are divided into three categories, the classification of which can only be determined by sampling the fluid: uncomplicated (simple), complicated, and empyema. **Uncomplicated (simple) parapneumonic effusions** are free-flowing sterile exudates of modest size that resolve quickly with antibiotic treatment of pneumonia. They do not need drainage.

Complicated parapneumonic effusions present the most difficult management decisions. They tend to be larger than simple parapneumonic effusions and to show more evidence of inflammatory stimuli, such as low glucose level, low pH, or evidence of loculation. Inflammation probably reflects ongoing bacterial invasion of the pleural space despite rare positive bacterial cultures. Tube thoracostomy is indicated when pleural fluid glucose is less than 60 mg/dL (less than 3.3 mmol/L), or the pH is less than 7.2. These thresholds have not been prospectively validated and should not be interpreted strictly. The clinician should consider drainage of a complicated effusion if the pleural fluid pH is between 7.2 and 7.3 or the LD is greater than 1000 units/L (greater than 20 mckat/L). Pleural fluid cell count and protein have little diagnostic value in this setting.

Empyema is gross infection of the pleural space indicated by positive Gram stain or culture. Empyema should be drained, and the patient referred to a thoracic specialist to determine whether tube thoracostomy versus decortication is needed to facilitate clearance of infection and to reduce the probability of permanent fibrous encasement of the lung.

Tube thoracostomy drainage of empyema or complicated parapneumonic effusions is frequently complicated by loculation that prevents adequate drainage. Intrapleural instillation of fibrinolytic agents alone has not been shown in controlled trials to improve drainage. The combination of intrapleural tissue plasminogen activator and deoxyribonuclease (DNase), an enzyme that catalyzes extracellular DNA and degrades biofilm formation within the pleural cavity, has been found to improve clinical outcome (increased drainage, decreased length of stay, and decreased surgical referral) compared with placebo or either agent alone, and should be considered when fever, leukocytosis, or anorexia persist despite antibiotics and tube thoracostomy, or when the lung fails to reexpand.

D. Hemothorax

A small-volume hemothorax that is stable or improving on chest radiographs may be managed by close observation. In all other cases, hemothorax is treated by immediate insertion of a thoracostomy tube to (1) drain existing blood and clot, (2) quantify the amount of bleeding, (3) reduce the risk of fibrothorax, and (4) permit apposition of the pleural surfaces to reduce hemorrhage. Thoracic surgery consultation is indicated. Thoracotomy may be required to control hemorrhage, remove clot, and treat complications.

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Bhatnagar R et al. Outpatient talc administration by indwelling pleural catheter for malignant effusion. N Engl J Med. 2018; 378:1313. [PMID: 29617585]
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Feller-Kopman D et al. Pleural disease. N Engl J Med. 2018;378: 740. [PMID: 29466146]
Thomas R et al. Management of malignant pleural effusions—what is new. Semin Respir Crit Care Med. 2019;40:323. [PMID: 31525808]

PNEUMOTHORAX

ESSENTIALS OF DIAGNOSIS

- Acute onset of unilateral chest pain and dyspnea.
- Minimal physical findings in mild cases; unilateral chest expansion, decreased tactile fremitus, hyperresonance, diminished breath sounds, mediastinal shift, cyanosis, and hypotension in tension pneumothorax.
- Presence of pleural air on chest radiograph.

General Considerations

Pneumothorax, or accumulation of air in the pleural space, is classified as spontaneous (primary or secondary), traumatic, or iatrogenic. **Primary spontaneous pneumothorax** occurs in the absence of an underlying lung disease, whereas **secondary spontaneous pneumothorax** is a complication of preexisting pulmonary disease. **Traumatic pneumothorax** results from penetrating or blunt trauma and includes **iatrogenic pneumothorax** following procedures, such as thoracentesis, pleural biopsy, subclavian or internal jugular vein catheter placement, percutaneous lung biopsy, bronchoscopy with transbronchial biopsy, and positive-pressure mechanical ventilation. **Tension pneumothorax** usually occurs in the setting of penetrating trauma, lung infection, CPR, or positive-pressure mechanical ventilation. In tension pneumothorax, the pressure of air in the pleural space exceeds alveolar and venous pressures throughout the respiratory cycle, resulting in compression of lung and reduction of venous return to the hemithorax; a check-valve mechanism may allow air to enter the pleural space on inspiration and to prevent egress of air on expiration.

Primary spontaneous pneumothorax is more likely among tall, thin individuals, more common in men, typically occurring at a young age (less than 45 years). It is thought to occur from rupture of subpleural apical blebs in response to high negative intrapleural pressures. Cigarette smoking is correlated with occurrence of primary

spontaneous pneumothorax, as are connective tissue disorders such as Marfan and Ehlers-Danlos syndromes.

Secondary pneumothorax occurs as a complication of COPD, interstitial lung disease, asthma, cystic fibrosis, tuberculosis, *Pneumocystis* pneumonia, necrotizing bacterial pneumonia, menstruation (catamenial pneumothorax), and a wide variety of cystic lung diseases, including lymphangioleiomyomatosis, tuberous sclerosis, Langerhans cell histiocytosis, and Birt-Hogg-Dube syndrome (a hereditary condition with multiple benign skin tumors, lung cysts, and increased risk of both benign and malignant kidney tumors). Secondary pneumothorax, particularly in patients with underlying symptomatic lung disease, is more poorly tolerated due to the decreased respiratory reserve in this group.

Clinical Findings

A. Symptoms and Signs

Chest pain ranging from minimal to severe on the affected side and dyspnea occur in nearly all patients, and cough is commonly reported. Pneumothorax may present with life-threatening respiratory failure if underlying lung disease is present or if tension pneumothorax physiology ensues.

If pneumothorax is small (less than 15% of a hemithorax), physical findings, other than mild tachycardia, are normal. If pneumothorax is large, diminished breath sounds, decreased tactile fremitus, decreased movement of the chest, and hyperresonant percussion note are often found. Tension pneumothorax should be suspected in the presence of marked tachycardia, hypotension, and mediastinal or tracheal shift.

B. Laboratory Findings

ABG analysis is often unnecessary but reveals hypoxemia and acute respiratory alkalosis in most patients. Left-sided primary pneumothorax may produce QRS axis and precordial T-wave changes on the ECG that may be misinterpreted as acute MI.

C. Imaging

Demonstration on chest radiograph of lucency without lung markings between the chest wall and lung, and visualization of the visceral pleura (a "pleural line") is diagnostic. A few patients have secondary pleural effusion that demonstrates a characteristic air-fluid level on chest radiography. In supine patients, pneumothorax on a conventional chest radiograph may appear as an abnormally radiolucent costophrenic sulcus (the "deep sulcus" sign). In patients with tension pneumothorax, chest radiographs show a large amount of air in the affected hemithorax and contralateral shift of the mediastinum.

Chest ultrasonography, performed at the bedside by experienced clinicians or technicians, demonstrates characteristic findings in the region of the pneumothorax. These findings include absent "lung sliding," or absent "lung pulse," or presence of a "lung point," all of which demonstrate a region of lung where the parietal and visceral pleural are not in normal apposition. Ultrasound may be more sensitive than supine chest radiograph (supine positioning necessitated by clinical circumstance) for detecting pneumothorax in trauma patients, and is frequently used in critical care, though comparisons of ultrasound to chest radiograph or to CT scan report variable test characteristics.

High-resolution CT may be considered with the first spontaneous pneumothorax to evaluate for underlying cystic lung disease.

Differential Diagnosis

If the patient is young with typical clinical characteristics, the diagnosis of primary spontaneous pneumothorax is usually obvious and can be confirmed by chest radiograph. Occasionally, pneumothorax may mimic MI, PE, or pneumonia.

Complications

Tension pneumothorax may be life-threatening. Pneumomediastinum and subcutaneous emphysema may occur as complications of spontaneous pneumothorax. If pneumomediastinum is detected, rupture of the esophagus or a bronchus should be considered in the differential diagnosis.

Treatment

Treatment depends on the severity of the pneumothorax and the nature of the underlying disease. In a reliable patient with a stable, spontaneous primary pneumothorax, observation alone may be appropriate; many cases resolve spontaneously as air is absorbed from the pleural space. In fact, a 2020 US study demonstrated that even moderate to large pneumothoraces in a stable patient (no oxygen requirement, no limitation to ambulation, and no increase in size of pneumothorax over 4 hours of monitoring) can be managed without intervention provided the patient is reliable. Simple aspiration drainage of pleural air with a small-bore catheter (eg, 16-gauge angiocatheter or larger drainage catheter) can be performed for spontaneous primary pneumothoraxes that are large or progressive. Placement of a small-bore chest tube (7F to 14F) attached to a one-way Heimlich valve provides protection against development of tension pneumothorax and may permit observation from home. The patient should be treated symptomatically for cough and chest pain and monitored with serial chest radiographs every 24 hours. Similarly, a 2021 observational report of pneumothorax following percutaneous lung biopsy found monitoring and noninvasive management to be sufficient in most patients.

Patients with secondary pneumothorax, tension pneumothorax, or severe symptoms or those who have a pneumothorax on mechanical ventilation should undergo chest tube placement (tube thoracostomy). The chest tube is placed under water-seal drainage, and suction is applied until the lung expands. The chest tube can be removed after the air leak subsides.

All patients who smoke should be advised to discontinue smoking and warned that the risk of recurrence is higher if cigarette smoking is continued.

Indications for surgical management (video-assisted thoracoscopic surgery) include recurrences of spontaneous pneumothorax, any occurrence of bilateral pneumothorax, and failure of tube thoracostomy for the first episode (failure of lung to reexpand or persistent air leak). Surgical intervention is also generally recommended for any patient with a secondary pneumothorax (presence of underlying lung disease) because the risk of recurrence is high, and the consequences of recurrences are greater. Surgery permits resection or repair of blebs or bullae responsible for the pneumothorax as well as mechanical or chemical pleurodesis. Patients who are not acceptable surgical candidates can be treated with chemical pleurodesis via a chest tube.

Prognosis

An average of 30% of patients with spontaneous pneumothorax experience recurrence of the disorder after either observation or tube thoracostomy for the first episode. Recurrence after surgical therapy is less frequent. Following successful therapy, there are no long-term complications. Secondary pneumothorax has up to a 50% likelihood of recurrence following the first event if surgical intervention is not undertaken.

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Chan KK et al. Chest ultrasonography versus supine chest radiography for diagnosis of pneumothorax in trauma patients in the emergency department. Cochrane Database Syst Rev. 2020;7:CD013031. [PMID: 32702777]
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DISORDERS OF CONTROL OF VENTILATION

The principal influences on ventilatory control are arterial P_{CO_2}, pH, P_{O_2}, and brainstem tissue pH. These variables are monitored by peripheral and central chemoreceptors. Under normal conditions, the ventilatory control system maintains arterial pH and P_{CO_2} within narrow limits; arterial P_{O_2} is more loosely controlled.

Abnormal control of ventilation can be seen with a variety of conditions ranging from rare disorders, such as primary alveolar hypoventilation, neuromuscular disorders, myxedema, starvation, and carotid body resection, to more common disorders, such as asthma, COPD, obesity, heart failure, and sleep-related breathing disorders. A few of these disorders will be discussed in this section.

HYPERVENTILATION SYNDROMES

Hyperventilation is an increase in alveolar minute ventilation that leads to hypocapnia. It may be caused by a variety of conditions, such as pregnancy, hypoxemia, obstructive and infiltrative lung diseases, sepsis, liver dysfunction, fever, and pain. Functional hyperventilation may be acute or chronic. **Acute hyperventilation** presents with hyperpnea, anxiety, paresthesias, carpopedal spasm, and tetany. **Chronic hyperventilation** may present with various nonspecific symptoms, including fatigue, dyspnea, anxiety, palpitations, and dizziness. The diagnosis of chronic hyperventilation syndrome is established if symptoms are reproduced during voluntary hyperventilation. Once organic causes of hyperventilation have been excluded, treatment of acute hyperventilation consists of breathing through pursed lips or through the nose with one nostril pinched or rebreathing expired gas from a paper bag held over the face to decrease respiratory alkalemia and its associated symptoms. Anxiolytic drugs may also be useful.

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Zhang Z et al. Hyperventilation in neurological patients: from physiology to outcome evidence. Curr Opin Anaesthesiol. 2019;32:568. [PMID: 31211719]

OBESITY-HYPOVENTILATION SYNDROME (Pickwickian Syndrome)

In obesity-hypoventilation syndrome, awake alveolar hypoventilation appears to result from a combination of blunted ventilatory drive and increased mechanical load imposed upon the chest by obesity. Voluntary hyperventilation returns the P_{CO_2} and the P_{O_2} toward normal values, a correction not seen in lung diseases causing chronic respiratory failure, such as COPD. Diagnostic criteria include a BMI greater than 30, an arterial partial pressure of carbon dioxide greater than 45 mm Hg, and exclusion of other causes of alveolar hypoventilation. Most patients with obesity-hypoventilation syndrome also suffer from obstructive sleep apnea, which must be treated aggressively if identified as a comorbid disorder. Therapy of obesity-hypoventilation syndrome consists mainly of weight loss, which improves hypercapnia and hypoxemia as well as the ventilatory responses to hypoxia and hypercapnia. Avoidance of sedative-hypnotics, opioids, and alcohol is also recommended. NIPPV is helpful in many patients. Patients with obesity-hypoventilation syndrome have a higher risk of complications in the perioperative period, including respiratory failure, intubation, and heart failure. Recognition of these patients in the perioperative period is an important safety measure.

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Mokhlesi B et al. Evaluation and management of obesity hypoventilation syndrome. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2019;200:e6. [PMID: 31368798]
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SLEEP-RELATED BREATHING DISORDERS

Abnormal ventilation during sleep is manifested by apnea (breath cessation for at least 10 seconds) or hypopnea (decrement in airflow with drop in hemoglobin saturation of at least 4%). Episodes of apnea are **central** if ventilatory effort is absent for the duration of the apneic episode, **obstructive** if ventilatory effort persists throughout the apneic episode but no airflow occurs because of transient obstruction of the upper airway, or **mixed** if absent ventilatory effort precedes upper airway obstruction during the apneic episode. Pure central sleep apnea is uncommon; it may be an isolated finding or may occur in patients with primary alveolar hypoventilation or with lesions of the brainstem. Obstructive and mixed sleep apneas are more common and may be associated with life-threatening cardiac arrhythmias, severe hypoxemia during sleep, daytime somnolence, pulmonary hypertension, right-sided heart failure, systemic hypertension, and secondary erythrocytosis.

Folmer RL et al. Prevalence and management of sleep disorders in the Veterans Health Administration. Sleep Med Rev. 2020; 54:101358. [PMID: 32791487]
Gandhi KD et al. Excessive daytime sleepiness: a clinical review. Mayo Clin Proc. 2021;96:1288. [PMID: 33840518]
McNicholas WT et al. Sleep in chronic respiratory disease: COPD and hypoventilation disorders. Eur Respir Rev. 2019; 28:190064. [PMID: 31554703]

OBSTRUCTIVE SLEEP APNEA

ESSENTIALS OF DIAGNOSIS

- Daytime somnolence or fatigue.
- A history of loud snoring with witnessed apneic events.
- Overnight polysomnography demonstrating apneic episodes with hypoxemia.

General Considerations

Upper airway obstruction during sleep occurs when loss of normal pharyngeal muscle tone allows the pharynx to collapse passively during inspiration. Patients with anatomically narrowed upper airways (eg, micrognathia, macroglossia, obesity, tonsillar hypertrophy) are predisposed to the development of obstructive sleep apnea. Ingestion of alcohol or sedatives before sleeping or nasal obstruction of any type, including the common cold, may precipitate or worsen the condition. Hypothyroidism and cigarette smoking are additional risk factors for obstructive sleep apnea. Before making the diagnosis of obstructive sleep apnea, a drug history should be obtained and a seizure disorder, narcolepsy, and depression should be excluded.

Clinical Findings

A. Symptoms and Signs

Most patients with obstructive or mixed sleep apnea are obese, middle-aged men. Arterial hypertension is common. Patients may complain of excessive daytime somnolence, morning sluggishness and headaches, daytime fatigue, cognitive impairment, recent weight gain, and impotence. Bed partners usually report loud cyclical snoring, breath cessation, witnessed apneas, restlessness, and thrashing movements of the extremities during sleep. Personality changes, poor judgment, work-related problems, depression, and intellectual deterioration (memory impairment, inability to concentrate) may also be observed. The USPSTF does not recommend screening asymptomatic adults for sleep apnea.

Physical examination may be normal or may reveal systemic and pulmonary hypertension with right-sided heart failure. The patient may appear sleepy or even fall asleep during the evaluation. The oropharynx is frequently found to be narrowed by excessive soft tissue folds, large tonsils, elongated uvula, or prominent tongue. Nasal obstruction by a deviated nasal septum, poor nasal airflow, and a nasal twang to the speech may be observed. A "bull neck" appearance is common.

B. Laboratory Findings

Erythrocytosis is common. Thyroid function tests (serum TSH, FT_4) should be obtained to exclude hypothyroidism.

C. Other Studies

Observation of the sleeping patient may reveal loud snoring interrupted by episodes of increasingly strong ventilatory effort that fail to produce airflow. A loud snort often accompanies the first breath following an apneic episode. Definitive diagnostic evaluation for suspected sleep apnea includes otorhinolaryngologic examination and overnight polysomnography (the monitoring of multiple physiologic factors during sleep). A complete **polysomnography** examination includes electroencephalography, electrooculography, electromyography, ECG, pulse oximetry, and measurement of respiratory effort and airflow. Polysomnography reveals apneic episodes lasting as long as 60 seconds. Oxygen saturation falls, often to very low levels. Bradydysrhythmias, such as sinus bradycardia, sinus arrest, or atrioventricular block, may occur. Tachydysrhythmias, including paroxysmal supraventricular tachycardia, atrial fibrillation, and ventricular tachycardia, may be seen once airflow is reestablished. Home sleep studies can be done for the person without comorbidities and a moderate to high pretest probability of obstructive sleep apnea. While home studies cannot quantify the stages of sleep, they can provide a reliable index of respiratory and desaturation events.

Treatment

Weight loss and strict avoidance of alcohol and hypnotic medications are the first steps in management. Weight loss may be curative, but most patients are unable to lose the 10–20% of body weight required. **Continuous positive airway pressure (CPAP)** at night is curative in many patients. Auto-titrating CPAP machines allow a range of pressures to be prescribed (5–15 cm H_2O). Polysomnography is frequently necessary to optimize the level of CPAP necessary to abolish obstructive apneas and manage hypoxemia. Unfortunately, only about 75% of patients continue to use nasal CPAP after 1 year. Supplemental oxygen may lessen the severity of nocturnal desaturation but may also lengthen apneas; it should not be routinely prescribed without polysomnography to assess the effects of oxygen therapy. Mechanical devices inserted into the mouth at bedtime to hold the jaw forward and prevent pharyngeal occlusion have modest effectiveness in relieving apnea. However, patient compliance with these devices is suboptimal.

Uvulopalatopharyngoplasty (UPPP), a procedure consisting of resection of pharyngeal soft tissue and amputation of approximately 15 mm of the free edge of the soft palate and uvula, is helpful in approximately 50% of selected patients. It is more effective in eliminating snoring than apneic episodes. UPPP may be performed on an outpatient basis with a laser. **Nasal septoplasty** is performed if gross anatomic nasal septal deformity is present. **Tracheostomy** relieves upper airway obstruction and its physiologic consequences and represents the definitive treatment for obstructive sleep apnea. However, it has numerous adverse effects, including granuloma formation, difficulty with speech, and stoma and airway infection. Furthermore, the long-term care of the tracheostomy, especially in obese patients, can be difficult. Tracheostomy and other maxillofacial surgery approaches are reserved for patients with life-threatening arrhythmias or severe disability who have not responded to conservative therapy. **Hypoglossal nerve stimulation** can be an option for select patients who do not respond to CPAP and have certain anatomic features, including nonconcentric airway collapse; a 5-year follow-up study showed improvement in sleepiness, quality of life, and respiratory outcomes in the treatment cohort. For patients who are unable or unwilling to use CPAP, and who may not be surgical candidates, the H_3-receptor antagonist/inverse agonist pitolisant has been shown to improve sleepiness and fatigue. Full normalization of breathing patterns is not necessarily the therapeutic goal. A randomized trial of adaptive servo-ventilation in sleep apnea patients with predominant central apnea and impaired LVEF (less than 45%) reported increased cardiovascular and all-cause mortality in the treatment group.

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Gottlieb DJ et al. Diagnosis and management of obstructive sleep apnea: a review. JAMA. 2020;323:1389. [PMID: 32286648]
Suurna MV et al. Obstructive sleep apnea: non-positive airway pressure treatments. Clin Geriatr Med. 2021;37:429. [PMID: 34210448]

ACUTE RESPIRATORY FAILURE

Respiratory failure is defined as respiratory dysfunction resulting in abnormalities of oxygenation or ventilation (CO_2 elimination) severe enough to threaten the function of vital organs. ABG criteria for respiratory failure are not absolute but may be arbitrarily established as a Po_2 under 60 mm Hg (7.8 kPa) or a Pco_2 over 50 mm Hg (6.5 kPa). Acute respiratory failure may occur in a variety of pulmonary and nonpulmonary disorders (Table 9–25). Only a few selected general principles of management will be reviewed here.

Clinical Findings

Symptoms and signs of acute respiratory failure are those of the underlying disease combined with those of hypoxemia or hypercapnia. The chief symptom of hypoxemia is dyspnea, though profound hypoxemia may exist in the absence of complaints. Signs of hypoxemia include cyanosis, restlessness, confusion, anxiety, delirium, tachypnea, bradycardia or tachycardia, hypotension or hypertension, cardiac dysrhythmias, and tremor. Dyspnea and headache are the cardinal symptoms of hypercapnia. Signs of hypercapnia include peripheral and conjunctival hyperemia, hypertension, tachycardia, tachypnea, impaired consciousness, papilledema, myoclonus, and asterixis. The symptoms and signs of acute respiratory failure are both insensitive and nonspecific; therefore, the clinician must maintain a high index of suspicion and obtain ABG analysis if respiratory failure is suspected.

Treatment

Treatment of the patient with acute respiratory failure consists of (1) specific therapy directed toward the underlying disease, (2) respiratory supportive care directed toward the maintenance of adequate gas exchange, and (3) general supportive care. Only the last two aspects are discussed below.

A. Respiratory Support

Respiratory support has both nonventilatory and ventilatory aspects.

1. Nonventilatory aspects—The main therapeutic goal in acute hypoxemic respiratory failure is to ensure adequate oxygenation of vital organs. Inspired oxygen concentration should be the lowest value that results in an arterial hemoglobin saturation of 88% (Po_2 55 mm Hg or 7.3 kPa) or more. Higher arterial oxygen tensions are of no proven benefit and may be deleterious. Restoration of normoxemia may rarely cause hypoventilation in patients with chronic hypercapnia; however, oxygen therapy should not be withheld for that concern. Hypoxemia in patients with obstructive airway disease is usually easily corrected by administering low-flow oxygen by nasal cannula (1–3 L/minute) or Venturi mask (24–40%). Higher concentrations of oxygen are necessary to correct hypoxemia in patients with ARDS, pneumonia, and other parenchymal lung diseases. Humidified, high-flow nasal cannulae provide

Table 9–25. Selected causes of acute respiratory failure in adults.

- **Airway disorders**
  - Asthma
  - Acute exacerbation of chronic bronchitis or emphysema
  - Obstruction of pharynx, larynx, trachea, mainstem bronchus, or lobar bronchus by edema, mucus, mass, or foreign body
- **Pulmonary edema**
  - Increased hydrostatic pressure
    - LV dysfunction (eg, myocardial ischemia, heart failure)
    - Mitral regurgitation
    - Left atrial outflow obstruction (eg, mitral stenosis)
    - Volume overload states
  - Increased pulmonary capillary permeability
    - Acute respiratory distress syndrome
    - Acute lung injury
  - Unclear etiology
    - Neurogenic
    - Negative pressure (inspiratory airway obstruction)
    - Re-expansion
    - Tocolytic-associated
- **Parenchymal lung disorders**
  - Pneumonia
  - Interstitial lung diseases
  - Diffuse alveolar hemorrhage syndromes
  - Aspiration
  - Lung contusion
- **Pulmonary vascular disorders**
  - Thromboembolism
  - Air embolism
  - Amniotic fluid embolism
- **Chest wall, diaphragm, and pleural disorders**
  - Rib fracture
  - Flail chest
  - Pneumothorax
  - Pleural effusion
  - Massive ascites
  - Abdominal distention and abdominal compartment syndrome
- **Neuromuscular and related disorders**
  - Primary neuromuscular diseases
    - Guillain-Barré syndrome
    - Myasthenia gravis
    - Poliomyelitis
    - Polymyositis
  - Drug- or toxin-induced
    - Botulism
    - Organophosphates
    - Neuromuscular blocking agents
    - Aminoglycosides
  - Spinal cord injury
  - Phrenic nerve injury or dysfunction
  - Electrolyte disturbances
    - Hypokalemia
    - Hypophosphatemia
  - Myxedema
- **CNS disorders**
  - Drugs: sedatives, hypnotics, opioids, anesthetics
  - Brainstem respiratory center disorders: trauma, tumor, vascular disorders, hypothyroidism
  - Intracranial hypertension
  - CNS infections
- **Increased CO_2 production**
  - Fever
  - Infection
  - Hyperalimentation with excess caloric and carbohydrate intake
  - Hyperthyroidism
  - Seizures
  - Rigors
  - Drugs

adjustable oxygen delivery and flow-dependent clearance of carbon dioxide from the upper airway, resulting in reduced work of breathing and better matching of respiratory demand during respiratory distress. In hypoxemia due to acute respiratory failure, oxygenation with use of humidified, high-flow nasal cannulae has been shown to be similar and, in some cases, superior to conventional low-flow oxygen supplementation and to NIPPV.

2. Ventilatory aspects—Ventilatory support consists of maintaining patency of the airway and ensuring adequate alveolar ventilation. Mechanical ventilation may be provided via mask (noninvasive) or through tracheal intubation.

A. Noninvasive positive-pressure ventilation—NIPPV delivered via a full-face mask or nasal mask is first-line therapy in COPD patients with hypercapnic respiratory failure who can protect and maintain the patency of their airway, handle their own secretions, and tolerate the mask apparatus. Several studies have demonstrated the effectiveness of this therapy in reducing intubation rates and ICU stays in patients with ventilatory failure. A bilevel positive-pressure ventilation mode is preferred for most patients. Patients with acute lung injury or ARDS or those who suffer from severely impaired oxygenation are less likely to benefit and should be intubated if they require mechanical ventilation.

B. Tracheal intubation—Indications for tracheal intubation include (1) hypoxemia despite supplemental oxygen; (2) upper airway obstruction; (3) impaired airway protection; (4) inability to clear secretions; (5) respiratory acidosis; (6) progressive general fatigue, tachypnea, use of accessory respiratory muscles, or mental status deterioration; and (7) apnea. Patients in respiratory failure who undergo a trial of NIPPV and do not improve within 30–90 minutes should be intubated. Of note, this practice changed somewhat during the COVID-19 pandemic—periods of high-level support, whether via humidified high-flow nasal cannula or NIPPV, are tolerated for longer in part due to resource limitations (lack of ventilators) and in part due to the frequency of patient self-induced lung injury while intubated. In general, orotracheal intubation is preferred to nasotracheal intubation in urgent or emergency situations because it is easier, faster, and less traumatic. The tip of the endotracheal tube should be positioned 2–4 cm above the carina and be verified by chest radiograph immediately following intubation. Only tracheal tubes with high-volume, low-pressure air-filled cuffs should be used. Cuff inflation pressure should be kept below 20 mm Hg, if possible, to minimize tracheal mucosal injury.

C. Mechanical ventilation—Indications for mechanical ventilation include (1) apnea, (2) acute hypercapnia that is not quickly reversed by appropriate specific therapy, (3) severe hypoxemia, and (4) progressive patient fatigue despite appropriate treatment.

Several modes of positive-pressure ventilation are available. Controlled mechanical ventilation (CMV; also known as assist-control [A-C]) and synchronized intermittent mandatory ventilation (SIMV) are ventilatory modes in which the ventilator delivers a minimum number of breaths of a specified pattern (either a set volume or a set pressure) each minute. In both CMV and SIMV, the patient may trigger the ventilator to deliver additional breaths. In CMV, the ventilator responds to breaths initiated by the patient above the set rate by delivering additional

full-support breaths. In SIMV, additional breaths are not supported by the ventilator unless the pressure support mode is added. Numerous alternative modes of mechanical ventilation now exist, the most popular being pressure support ventilation (PSV), proportional-assist ventilation, and CPAP.

Positive end-expiratory pressure (PEEP) is useful in improving oxygenation in patients with diffuse parenchymal lung disease, such as ARDS. It should be used cautiously in patients with localized parenchymal disease, emphysema, hyperinflation, or very high airway pressure requirements during mechanical ventilation.

D. Complications of Mechanical Ventilation— Potential complications of mechanical ventilation are numerous. Migration of the tip of the endotracheal tube into a main bronchus can cause atelectasis of the contralateral lung and overdistention of the intubated lung. Barotrauma refers to rupture and loss of integrity of the alveolar space secondary to high transmural pressures applied during positive-pressure ventilation. Barotrauma is manifested by subcutaneous emphysema, pneumomediastinum, subpleural air cysts, pneumothorax, or systemic gas embolism. Volutrauma is sometimes used to refer to subtle parenchymal injury due to overdistention of alveoli from excessive tidal volumes without alveolar rupture, mediated through inflammatory rather than physical mechanisms. The principal strategy to avoid volutrauma is the use of low tidal volume ventilation (a tidal volume of 6 mL/kg of ideal body weight is supported by the ARDS literature).

Acute respiratory alkalosis caused by overventilation is common. Hypotension induced by elevated intrathoracic pressure that results in decreased return of systemic venous blood to the heart may occur in patients treated with PEEP, particularly those with intravascular volume depletion, and in patients with severe airflow obstruction at high respiratory rates that promote dynamic hyperinflation ("breath stacking"). Ventilator-associated pneumonia is another serious complication of mechanical ventilation.

B. General Supportive Care

Hypokalemia and hypophosphatemia may worsen hypoventilation due to respiratory muscle weakness. Sedative-hypnotics and opioid analgesics should be titrated carefully to avoid oversedation, leading to prolongation of intubation. Temporary paralysis with a nondepolarizing neuromuscular blocking agent is used to facilitate mechanical ventilation and to lower oxygen consumption. Prolonged muscle weakness due to an acute myopathy is a potential complication of these agents. Myopathy is more common in patients with kidney injury and in those given concomitant corticosteroids.

Psychological and emotional support of the patient and family, skin care to avoid pressure injuries, and meticulous avoidance of health care–associated infection and complications of endotracheal tubes are vital aspects of comprehensive care for patients with acute respiratory failure.

Attention must also be paid to preventing complications associated with serious illness. Stress gastritis and ulcers may be avoided by administering sucralfate, histamine H_2-receptor antagonists, or PPIs. Meta-analyses have demonstrated that PPIs are most effective. The risk of DVT and PE may be reduced by subcutaneous administration of heparin or low-molecular-weight heparin (LMWH) (see Table 14–14), or placement of sequential compression devices on the lower extremities.

Course & Prognosis

The course and prognosis of acute respiratory failure vary and depend on the underlying disease. The prognosis of acute respiratory failure caused by uncomplicated sedative or opioid overdose is excellent. Acute respiratory failure in patients with COPD who do not require intubation and mechanical ventilation has a good immediate prognosis. On the other hand, ARDS and respiratory failure associated with sepsis have a poor prognosis.

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Grieco DL et al. Physiological comparison of high-flow nasal cannula and helmet noninvasive ventilation in acute hypoxemic respiratory failure. Am J Respir Crit Care Med. 2020; 201:303. [PMID: 31687831]

Richards H et al. Clinical benefits of prone positioning in the treatment of non-intubated patients with acute hypoxic respiratory failure: a rapid systematic review. Emerg Med J. 2021; 38:594. [PMID: 34162630]

Rochwerg B et al. High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. Intensive Care Med. 2019;45:563. [PMID: 30888444]

Schjørring OL et al; HOT-ICU Investigators. Lower or higher oxygenation targets for acute hypoxemic respiratory failure. N Engl J Med. 2021;384:1301. [PMID: 33471452]

ACUTE RESPIRATORY DISTRESS SYNDROME

ESSENTIALS OF DIAGNOSIS

- Onset of respiratory distress, often progressing to respiratory failure, within 7 days of a known clinical insult.
- New, bilateral radiographic pulmonary opacities not explained by pleural effusion, atelectasis, or nodules.
- Respiratory failure not fully explained by heart failure or volume overload.
- Impaired oxygenation, with ratio of partial pressure of oxygen in arterial blood (Pao_2) to fractional concentration of inspired oxygen (Fio_2) < 300 mm Hg, with PEEP ≥ 5 cm H_2O.

General Considerations

Acute respiratory distress syndrome (ARDS) as a clinical syndrome is based on three inclusion criteria plus one

Table 9–26. Selected disorders associated with ARDS.

Systemic Insults	Pulmonary Insults
Trauma	Aspiration of gastric contents
Sepsis	Embolism of thrombus, fat, air, or amniotic fluid
Pancreatitis	Miliary tuberculosis
Shock	Diffuse pneumonia (eg, SARS, COVID-19)
Multiple transfusions	Acute eosinophilic pneumonia
Disseminated intravascular coagulation	Cryptogenic organizing pneumonitis
Burns	Upper airway obstruction
Drugs and drug overdose	Free-base cocaine smoking
Opioids	Near-drowning
Aspirin	Toxic gas inhalation
Phenothiazines	Nitrogen dioxide
Tricyclic antidepressants	Chlorine
Amiodarone	Sulfur dioxide
Chemotherapeutic agents	Ammonia
Nitrofurantoin	Smoke
Protamine	Oxygen toxicity
Thrombotic thrombocytopenic purpura	Lung contusion
Cardiopulmonary bypass	Radiation exposure
Head injury	High-altitude exposure
Paraquat	Lung reexpansion or reperfusion

ARDS, acute respiratory distress syndrome; SARS, severe acute respiratory syndrome.

exclusion criterion, as detailed above. The severity of ARDS is based on the level of oxygenation impairment: **mild,** Pao_2/Fio_2 ratio between 200 mm Hg and 300 mm Hg; **moderate,** Pao_2/Fio_2 ratio between 100 mm Hg and 200 mm Hg; and **severe,** Pao_2/Fio_2 ratio less than 100 mm Hg.

ARDS may follow a wide variety of clinical events (Table 9–26). Common risk factors for ARDS include sepsis, aspiration of gastric contents, shock, infection, lung contusion, nonthoracic trauma, toxic inhalation, near-drowning, and multiple blood transfusions. About one-third of ARDS patients initially have sepsis syndrome. Damage to capillary endothelial cells and alveolar epithelial cells is common to ARDS regardless of cause or mechanism of lung injury and results in increased vascular permeability and decreased production and activity of surfactant. These abnormalities in turn lead to interstitial and alveolar pulmonary edema, alveolar collapse, and hypoxemia.

Clinical Findings

ARDS is marked by the rapid onset of profound dyspnea that usually occurs 12–48 hours after the initiating event. Labored breathing, tachypnea, intercostal retractions, and crackles are noted on physical examination. Chest radiography shows diffuse or patchy bilateral infiltrates that rapidly become confluent; these characteristically spare the costophrenic angles. Air bronchograms occur in about 80% of cases. Heart size is usually normal, and pleural effusions are small or nonexistent. Marked hypoxemia occurs that is refractory to treatment with supplemental oxygen. Many patients with ARDS demonstrate multiple organ failure, particularly involving the kidneys, liver, gut, CNS, and cardiovascular system.

Differential Diagnosis

Since ARDS is a physiologic and radiographic syndrome rather than a specific disease, the concept of differential diagnosis does not strictly apply. Normal-permeability ("cardiogenic" or hydrostatic) pulmonary edema must be excluded, however, because specific therapy is available for that disorder. Emergent echocardiogram or measurement of pulmonary capillary wedge pressure by means of a flow-directed pulmonary artery catheter may be required in selected patients with suspected cardiac dysfunction; routine use in ARDS is discouraged.

Prevention

No measures that effectively prevent ARDS have been identified. Specifically, neither PEEP nor aspirin when used prophylactically has been shown to be effective in patients at risk for ARDS. Intravenous methylprednisolone does not prevent ARDS when given early to patients with sepsis syndrome or septic shock.

Treatment

The first principle in management is to identify and treat the primary condition that has led to ARDS. Meticulous supportive care must then be provided to compensate for the severe dysfunction of the respiratory system associated with ARDS and to prevent complications.

Treatment of the hypoxemia seen in ARDS usually requires tracheal intubation and positive-pressure mechanical ventilation. The lowest levels of PEEP (used to recruit atelectatic alveoli) and supplemental oxygen required to maintain the Pao_2 above 55 mm Hg (7.13 kPa) or the Sao_2 above 88% should be used. Efforts should be made to decrease Fio_2 as soon as possible to avoid oxygen toxicity. PEEP can be increased as needed if cardiac output and oxygen delivery do not decrease and airway pressures do not increase excessively (ie, plateau pressures remain below 30 cm H_2O). Prone positioning frequently improves oxygenation by helping recruit atelectatic alveoli and has been shown in some (although not all) trials to provide a mortality benefit in severe ARDS. Routine use of neuromuscular blockade is controversial; one major trial showed improved mortality and more ventilator-free days in patients with Pao_2/Fio_2 ratio less than 120 mm Hg but a subsequent trial (intended to be confirmatory) did not demonstrate a mortality benefit.

A variety of mechanical ventilation strategies are available. The most significant advance in the treatment of ARDS over the past 20 years has been the recognition of the potential for excessive alveolar stretch to cause lung injury, and the widespread adoption of low tidal volume ventilation. A multicenter study of 800 patients demonstrated that a protocol using volume-control ventilation with low tidal volumes (6 mL/kg of ideal body weight) resulted in an 8.8% absolute mortality reduction over therapy with standard tidal volumes (defined as 12 mL/kg of ideal body weight). Varying ventilator modes have been

used; conventional modes of ventilation are essentially equivalent, while high-frequency oscillatory ventilation should not be used an as initial mode.

Approaches to hemodynamic monitoring and fluid management in patients with acute lung injury have been carefully studied. A prospective RCT comparing hemodynamic management guided either by a pulmonary artery catheter or a central venous catheter using an explicit management protocol demonstrated that a pulmonary artery catheter should not be routinely used for the management of acute lung injury. A subsequent randomized, prospective clinical study of restrictive fluid intake and diuresis as needed to maintain central venous pressure less than 4 mm Hg or pulmonary artery occlusion pressure less than 8 mm Hg (conservative strategy group) versus a fluid management protocol to target a central venous pressure of 10–14 mm Hg or a pulmonary artery occlusion pressure 14–18 mm Hg (liberal strategy group) showed that patients in the conservative strategy group experienced faster improvement in lung function and spent significantly fewer days on mechanical ventilation and in the ICU without an improvement in death by 60 days or worsening nonpulmonary organ failure at 28 days. Oxygen delivery can be increased in anemic patients by ensuring that the hemoglobin concentration is at least 7 g/dL (70 g/L); patients are not likely to benefit from higher levels. Increasing oxygen delivery to supranormal levels by using inotropes and high hemoglobin concentrations is not clinically useful and may be harmful. Strategies to decrease oxygen consumption include the appropriate use of sedatives, analgesics, and antipyretics.

Numerous innovative therapeutic interventions to improve outcomes in ARDS patients have been or are being investigated. Unfortunately, to date, none has consistently shown benefit in clinical trials. Systemic corticosteroids have been studied extensively with variable and inconsistent results. While a few small studies suggest some specific improved outcomes when given within the first 2 weeks after the onset of ARDS, mortality appears increased when corticosteroids are started more than 2 weeks after the onset of ARDS. Therefore, routine use of corticosteroids is not recommended.

Another therapeutic intervention is extracorporeal membrane oxygenation (ECMO). The technique has been in use since the 1970s but has been gaining wider acceptance. A 2018 trial compared the early use of ECMO in very severe ARDS with conventional strategies built on low-tidal-volume ventilation. Results failed to show a difference in 60-day mortality; however, 28% of the control group crossed over to receive ECMO. As a result, ECMO seems unlikely to become a standard first-line therapy but is likely to remain a salvage option for patients with very severe ARDS.

Course & Prognosis

Overall, ARDS mortality with low tidal volume ventilation is around 30% in large multicenter studies. The major causes of death are the primary illness and secondary complications, such as multiple organ system failure or sepsis. Many patients who die of ARDS and its complications die after withdrawal of mechanical ventilation (see Chapter 5). One troubling aspect of ARDS care is that the actual mortality of ARDS in community hospitals continues to be higher than at academic hospitals. This may reflect the fact that a significant number of community hospital–based clinicians have not adopted low tidal volume ventilation.

Different clinical syndromes that lead to ARDS carry different prognoses. For example, patients with trauma-associated ARDS have better prognosis, with a mortality rate close to 20%, whereas those with end-stage liver disease have an 80% mortality rate. This likely reflects both the effects of significant comorbidities (trauma patients tend to be younger and healthier) as well as phenotypic differences within ARDS associated with different precipitants. Post-hoc analyses of data from several major trials have shown that a hyperinflammatory phenotype associated with high levels of IL-6 and soluble tumor necrosis factor receptor in ARDS patients precipitated by sepsis is associated with more multiorgan dysfunction and higher mortality. This may have implications for precision-medicine treatment of ARDS.

Failure to improve in the first week of treatment is a poor prognostic sign, although this may not be true of ARDS from certain etiologies, including COVID-19. Survivors tend to be young and pulmonary function generally recovers over 6–12 months, although residual abnormalities often remain, including restrictive or obstructive defects, low diffusion capacity, and impaired gas exchange with exercise. Survivors of ARDS also have diminished health-related and pulmonary disease–specific quality of life as well as systemic effects, such as muscle wasting, weakness, and fatigue.

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Matthay MA et al. Acute respiratory distress syndrome. Nat Rev Dis Primers. 2019;5:18. [PMID: 30872586]

Meyer NJ et al. Acute respiratory distress syndrome. Lancet. 2021;398:622. [PMID: 34217425]

National Heart, Lung, and Blood Institute PETAL Clinical Trials Network; Moss M et al. Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med. 2019; 380:1997. [PMID: 31112383]

Papazian L et al. Formal guidelines: management of acute respiratory distress syndrome. Ann Intensive Care. 2019;9:69. [PMID: 31197492]

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LUNG TRANSPLANTATION

Introduction

Lung transplantation is a therapeutic option for patients with end-stage lung disease who have not responded to other therapies. The full topic is beyond the scope of this text, therefore only issues related to candidate selection and post-transplant care will be discussed.

Candidate Selection

Patients should be considered for lung transplantation if they have advanced, progressive lung disease despite appropriate medical therapy. The most common indications are interstitial lung disease, COPD, cystic fibrosis, and pulmonary arterial hypertension. The International Society of Heart and Lung Transplantation has produced guidelines for candidate selection; broadly speaking, the ideal candidate has a high (greater than 50%) risk of dying within 2 years without lung transplantation, has minimal other comorbidities, is very likely to survive transplantation, and has good social support. Contraindications are numerous and include obesity (generally BMI greater than 30 is a relative, and greater than 35 a nearly absolute, contraindication), active smoking or substance abuse, uncontrolled infection, active malignancy, significant organ dysfunction (eg, cirrhosis, CKD, heart failure, unrevascularizable coronary disease), and medical noncompliance. Each transplant center has a slightly different selection process, however common practice includes a detailed multidisciplinary evaluation. Patients should ideally be referred to transplant centers before the need for transplantation is emergent.

Care After Transplantation

As with other solid organ transplantation, care of the post–lung transplant patient is particularly concerned with immunosuppression and prophylaxis against infection, as well as with management of the side effects of immunosuppression. Most patients are immunosuppressed with a combination of a calcineurin inhibitor (eg, tacrolimus), a cell-cycle inhibitor (eg, mycophenolate mofetil), and glucocorticoids. Most centers screen for rejection with regular PFTs as well as bronchoscopies and biopsies, particularly in the first 1–2 years after transplantation.

Common complications include acute cellular rejection (treated with intensified immunosuppression), infection, chronic rejection (for which few effective treatments exist), and sequelae of immunosuppression. These include hypertension, dyslipidemia, diabetes mellitus, CKD, osteopenia/osteoporosis, and increased risk of malignancy, especially skin cancers. Post-transplant care thus necessitates close cooperation between the patient's transplant team and his or her other physicians.

Outcomes After Transplantation

While lung transplantation can be transformative for those suffering from advanced lung disease, long-term survival remains limited to those receiving kidney or liver transplants. As of the 2021 International Society of Heart and Lung Transplantation Report, median survival after lung transplantation was approximately 7 years. Survival is affected by many variables; two consistent findings have been that survival is improved in double (versus single) lung transplant patients, and in those transplanted for cystic fibrosis (versus other indications).

Bos S et al. Survival in adult lung transplantation: where are we in 2020? Curr Opin Organ Transplant. 2020;25:268. [PMID: 32332197]

Chambers DC et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-Eighth Adult Lung Transplantation Report—2021; Focus on recipient characteristics. J Heart Lung Transplant. 2021;40:1060. [PMID: 34446355]

Gutierrez-Arias R et al. Exercise training for adult lung transplant recipients. Cochrane Database Syst Rev. 2021;7:CD012307. [PMID: 34282853]

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Heart Disease

10

Todd Kiefer, MD
Christopher B. Granger, MD
Kevin P. Jackson, MD

ADULT CONGENITAL HEART DISEASE

In the United States, there are many more adults with congenital heart disease than children, with an estimated 2 million adults in the United States surviving with congenital heart disease. In 2018, the American College of Cardiology (ACC) and American Heart Association (AHA) released updated guidelines for the assessment and treatment of patients with adult congenital heart disease. The European Society of Cardiology (ESC) completed their update on the same topic in 2020. As the number of patients with adult congenital heart disease has grown, there has been an increased appreciation of the need for more training and guidelines. A specific subspecialty board and training program has been established. The AHA also issued a scientific statement in 2015 reviewing common issues for adults with underlying congenital heart disease, another statement in 2017 for pregnant patients with congenital heart disease, and a statement in 2017 regarding noncardiac issues in these patients.

Baumgartner H et al. 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Heart J. 2021;42:563. [PMID: 32860028]

Stout KK et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73:e81. [PMID: 30121239]

PULMONARY VALVE STENOSIS

ESSENTIALS OF DIAGNOSIS

- Severe cases may present with right-sided heart failure.
- P_2 delayed and soft or absent.
- Pulmonary ejection click often present and decreases with inspiration—the only right heart sound that *decreases* with inspiration; all other right heart sounds increase.
- Echocardiography/Doppler is diagnostic.
- Patients with peak pulmonic valve gradient greater than 64 mm Hg or a mean of 35 mm Hg by echocardiography/Doppler should undergo intervention regardless of symptoms. Otherwise, operate for symptoms or evidence for right ventricular (RV) dysfunction.

General Considerations

Stenosis of the pulmonary valve or RV infundibulum increases the resistance to RV outflow, raises the RV pressure, and limits pulmonary blood flow. Pulmonic stenosis is often congenital and associated with other cardiac lesions. Pulmonary blood flow preferentially goes to the left lung in valvular pulmonic stenosis. In the absence of associated shunts, arterial saturation is normal. Peripheral pulmonic stenosis can accompany valvular pulmonic stenosis and may be part of a variety of clinical syndromes, including the congenital rubella syndrome. Patients who have had the **Ross procedure** for aortic valve disease (transfer of the pulmonary valve to the aortic position with a homograft pulmonary valve placed in the pulmonary position) may experience noncongenital postoperative pulmonic valvular or main pulmonary artery (PA) stenosis due to an immune response in the homograft. RV outflow obstructions can also occur when there is a conduit from the RV to the pulmonary artery that becomes stenotic from degenerative changes over time or when there is degeneration of a bioprosthetic replacement pulmonary valve.

Clinical Findings

A. Symptoms and Signs

Mild cases of pulmonic stenosis are asymptomatic; moderate to severe pulmonic stenosis may cause symptoms of dyspnea on exertion, syncope, chest pain, and eventually RV failure.

On examination, there is often a palpable parasternal lift due to right ventricular hypertrophy (RVH) and the pulmonary outflow tract may be palpable if the PA is enlarged. A loud, harsh systolic murmur and occasionally a prominent thrill are present in the left second and third

interspaces parasternally. The murmur radiates toward the left shoulder due to the flow pattern within the main PA and increases with inspiration. In mild to moderate pulmonic stenosis, a loud ejection click can be heard to precede the murmur; this sound decreases with inspiration as the increased RV filling from inspiration prematurely opens the valve during atrial systole when inspiratory increased blood flow to the right heart occurs. The valve excursion during systole is thus less with inspiration than with expiration, and the click is therefore less audible with inspiration. *This is the only right-sided auscultatory event that decreases with inspiration.* All of the other auscultatory events increase with the increased right heart output that occurs with inspiration. In severe pulmonic stenosis, the second sound is obscured by the murmur and the pulmonary component of S_2 may be diminished, delayed, or absent. A right-sided S_4 and a prominent *a* wave in the venous pulse are present when there is RV diastolic dysfunction or a *c-v* wave may be observed in the jugular venous pressure if tricuspid regurgitation is present. Pulmonary valve regurgitation is relatively uncommon in primary pulmonic stenosis and may be very difficult to hear, as the gradient between the reduced PA diastolic pressure and the elevated RV diastolic pressure may be quite small (low-pressure pulmonary valve regurgitation).

B. ECG and Chest Radiography

Right axis deviation or RVH is noted; peaked P waves provide evidence of right atrial (RA) overload. Heart size may be normal on radiographs, or there may be a prominent RV and RA or gross cardiac enlargement, depending on the severity. There is often poststenotic dilation of the main and left pulmonary arteries. Pulmonary vascularity is usually normal, although there tends to be preferential flow to the left lung.

C. Diagnostic Studies

Echocardiography/Doppler is the diagnostic tool of choice, can provide evidence for a doming valve versus a dysplastic valve, can determine the gradient across the valve, and can provide information regarding subvalvular obstruction and the presence or absence of tricuspid or pulmonic valvular regurgitation. Mild pulmonic stenosis is present if the peak gradient by echocardiography/Doppler is less than 36 mm Hg, moderate pulmonic stenosis is present if the peak gradient is between 36 mm Hg and 64 mm Hg, and severe pulmonic stenosis is present if the peak gradient is greater than 64 mm Hg or the mean gradient is greater than 35 mm Hg. A lower gradient may be significant if there is RV dysfunction. Catheterization is usually unnecessary for the diagnosis; it should be used only if the data are unclear or in preparation for either percutaneous intervention or surgery.

Prognosis & Treatment

Patients with mild pulmonic stenosis have a normal life span with no intervention. Moderate stenosis may be asymptomatic in childhood and adolescence, but symptoms often appear as patients grow older. The degree of stenosis does worsen with time in a few patients, so serial follow-up is important. Severe stenosis is rarely associated with sudden death but can cause right heart failure in patients as early as in their 20s and 30s. Pregnancy and exercise tend to be well tolerated except in severe stenosis.

The AHA/ACC guidelines and the ESC guidelines generally agree, though the ESC suggests severe pulmonic stenosis should be considered if the RV systolic pressure is greater than 80 mm Hg. Class I (definitive) indications for intervention include all symptomatic patients and all those with a resting peak-to-peak gradient greater than 64 mm Hg or a mean greater than 35 mm Hg, regardless of symptoms. Symptoms can include cyanosis due to right-to-left shunting via a patent foramen ovale (PFO) or atrial septal defect (ASD). Percutaneous balloon valvuloplasty is highly successful in domed valve patients and is the treatment of choice. Surgical commissurotomy can also be done, or pulmonary valve replacement (with either a bioprosthetic valve or homograft) when pulmonary valve regurgitation is too severe or the valve is dysplastic. Pulmonary outflow tract obstruction due to RV to PA conduit obstruction or to homograft pulmonary valve stenosis can often be relieved with a percutaneously implanted pulmonary valve (both the Medtronic Melody valve and the Edwards Sapien XT valve are FDA approved). Frequently the seating of these valves is facilitated by placing a stent within the pulmonary artery first, then the transcatheter device within this stent. Because the new catheter valve may result in compression of the coronary artery, it is a class I requirement to assess the effect of the device on the coronary by use of a temporary balloon inflation prior to delivery of the device. Percutaneous pulmonary valve replacement is also FDA approved for those with conduit stenosis or following the Ross procedure. Percutaneous valve replacements have also been performed off-label for patients with native pulmonary valve disease, including those who have had tetralogy of Fallot repair (assuming the PA root size is small enough to seat a percutaneous valve).

Endocarditis prophylaxis is unnecessary for native valves even after valvuloplasty unless there has been prior pulmonary valve endocarditis (an unusual occurrence) (see Table 33–3). It should be used if surgical or percutaneous valve replacement has occurred. There appears to be more pulmonary valve endocarditis following percutaneous pulmonary valve replacement with the Melody valve than expected, and this is being closely monitored by the FDA.

When to Refer

All symptomatic patients (regardless of gradient) and all asymptomatic patients whose peak pulmonary valve gradient is greater than 64 mm Hg or whose mean gradient is greater than 35 mm Hg should be referred to a cardiologist with expertise in adult congenital heart disease. Patients also require intervention if cyanosis occurs due to a PFO or ASD or if there is exercise intolerance.

Hansen RL et al. Long-term outcomes up to 25 years following balloon pulmonary valvuloplasty: a multicenter study. Congenit Heart Dis. 2019;14:1037. [PMID: 31250555]

COARCTATION OF THE AORTA

ESSENTIALS OF DIAGNOSIS

- Usual presentation is systemic hypertension.
- Echocardiography/Doppler is diagnostic; a peak gradient of > 20 mm Hg may be significant due to collaterals around the coarctation reducing gradient despite severe obstruction.
- Associated bicuspid aortic valve in 50–80% of patients.
- Delayed pulse in femoral artery compared to brachial artery.
- Systolic pressure is higher in upper extremities than in lower extremities; diastolic pressures are similar.

General Considerations

Coarctation of the aorta consists of localized narrowing of the aortic arch just distal to the origin of the left subclavian artery. If the stenosis is severe, collateral circulation develops around the coarctation site through the intercostal arteries and the branches of the subclavian arteries and can result in a lower trans-coarctation gradient by enabling blood flow to bypass the obstruction. **Coarctation is a cause of secondary hypertension and should be considered in young patients with elevated blood pressure (BP).** The renin-angiotensin system is often abnormal, however, and contributes to the hypertension occasionally seen even after coarctation repair. A bicuspid valve is seen in approximately 50–80% of the cases, and there is an increased incidence of cerebral berry aneurysms. Significant native or recurrent aortic coarctation has been defined as follows: upper extremity/lower extremity resting peak-to-peak gradient greater than 20 mm Hg or mean Doppler systolic gradient greater than 20 mm Hg; upper extremity/lower extremity gradient greater than 10 mm Hg or mean Doppler gradient greater than 10 mm Hg when there is either decreased LV systolic function or aortic regurgitation (AR); or upper extremity/lower extremity gradient greater than 10 mm Hg or mean Doppler gradient greater than 10 mm Hg when there is evidence for collateral flow around the coarctation. This should be coupled with anatomic evidence for coarctation of the aorta, typically defined by advanced imaging (cardiac magnetic resonance, CT angiography). The ESC guidelines have expanded the severity criteria and suggest stenting is appropriate if the patient is normotensive but has a peak gradient of greater than 20 mm Hg (class IIa) or if the stenosis by angiography is more than 50% (class IIb).

Clinical Findings

A. Symptoms and Signs

If cardiac failure does not occur in infancy, there are usually no symptoms until the hypertension produces LV failure. Cerebral hemorrhage, though rare, may occur. Approximately 10% of patients with coarctation of the aorta have intracranial aneurysms identified on magnetic resonance angiography or CT angiography. Increasing age has been identified as a risk factor. Strong arterial pulsations are seen in the neck and suprasternal notch. Hypertension is present in the arms, but the pressure is normal or low in the legs. This difference is exaggerated by exercise. Femoral pulsations are weak and are delayed in comparison with the brachial or radial pulse. A continuous murmur heard superiorly and midline in the back or over the left anterior chest may be present when large collaterals are present and is a clue that the coarctation is severe. The coarctation itself may result in systolic ejection murmurs heard in the left upper lung field anteriorly and near the spine on the left side posteriorly. There may be an aortic regurgitation or stenosis murmur due to an associated bicuspid aortic valve. Coarctation is associated with Turner syndrome (a sex chromosomal abnormality [XO]); a webbed neck may be present in these patients.

B. ECG and Chest Radiography

The ECG usually shows LVH. Radiography may show scalloping of the inferior portion of the ribs (**rib notching**) due to enlarged collateral intercostal arteries. Dilation of the left subclavian artery and poststenotic aortic dilation along with LV enlargement may be present. The coarctation region and the poststenotic dilation of the descending aorta may result in a **"3" sign** along the aortic shadow on the PA chest radiograph (the notch in the "3" representing the area of coarctation).

C. Diagnostic Studies

Echocardiography/Doppler is usually diagnostic and may provide additional evidence for a bicuspid aortic valve. Both MRI and CT can provide excellent images of the coarctation anatomy, and one or the other should always be done to define the coarctation anatomic structure. MRI and echocardiography/Doppler can also provide estimates of the gradient across the lesion. Cardiac catheterization provides definitive gradient information and is obviously necessary if percutaneous stenting is to be considered.

Prognosis & Treatment

Cardiac failure is common in infancy and in older untreated patients when the coarctation is severe. Patients with a demonstrated peak gradient of greater than 20 mm Hg should be considered for intervention, especially if there is evidence of collateral blood vessels. As noted above, the ESC guidelines incorporate the stenosis severity (greater than 50%) as defining severe coarctation as well. Many untreated patients with severe coarctation die of hypertension, rupture of the aorta, infective endarteritis, or cerebral hemorrhage before the age of 50. Aortic dissection also occurs with increased frequency. Coarctation of any significance may be poorly tolerated in pregnancy because of the inability to support the placental flow.

Resection of the coarctation site has a surgical mortality rate of 1–4% and includes risk of spinal cord injury.

The percutaneous interventional procedure of choice is endovascular stenting; when anatomically feasible, self-expanding and balloon-expandable covered stents have been shown to be advantageous over bare metal stents. These covered stents are FDA approved. Most coarctation repair in adults is percutaneous. Otherwise, surgical resection (usually with end-to-end anastomosis) should be performed. About 25–50% of surgically corrected patients continue to be hypertensive years after surgery because of permanent changes in the renin-angiotensin system, endothelial dysfunction, aortic stiffness, altered arch morphology, and increased ventricular stiffness. Whether the repair was by balloon dilatation, stenting, or surgical resection may make a difference in the development of hypertension. Recurrence of the coarctation stenosis following intervention requires long-term follow-up.

When to Refer

All patients with aortic coarctation and any detectable gradient should be referred to a cardiologist with expertise in adult congenital heart disease.

Fedchenko M et al. Cardiovascular risk factors in adults with coarctation of the aorta. Congenit Heart Dis. 2019;14:549. [PMID: 31099471]

Lee MGY et al. Long-term mortality and cardiovascular burden for adult survivors of coarctation of the aorta. Heart. 2019;105:1190. [PMID: 30923175]

ATRIAL SEPTAL DEFECT & PATENT FORAMEN OVALE

ESSENTIALS OF DIAGNOSIS

- Often asymptomatic and discovered on routine physical examination.
- With an ASD and left-to-right shunt: RV lift; S2 widely split and fixed.
- Echocardiography/Doppler is diagnostic.
- ASDs should be closed if there is evidence of an RV volume overload regardless of symptoms.
- A PFO, present in 25% of the population, rarely can lead to paradoxical emboli.

General Considerations

The most common form of ASD (80% of cases) is persistence of the ostium secundum in the mid-septum. A less common abnormality is persistence of the ostium primum (low in the septum). In most patients with an ostium primum defect, there are mitral or tricuspid valve "clefts" as well as a ventricular septal defect (VSD) as part of the atrioventricular (AV) septal defect. A sinus venosus defect is a hole, usually at the upper (or rarely the lower) part of the atrial septum, due to failure of the embryonic superior vena cava or the inferior vena cava to merge with the atria properly. The superior vena cava sinus venosus defect is usually associated with an anomalous connection of the right upper pulmonary vein into the superior vena cava. The coronary sinus ASD is rare and is basically an unroofed coronary sinus that results in shunting from the left atrium (LA) to the coronary sinus and then to the RA.

In all cases, normally oxygenated blood from the higher-pressure LA shunts into the RA, increasing RV output and pulmonary blood flow. In children, the degree of shunting across these defects may be quite large (pulmonary to systemic blood flow ratios of 3:1 or so). As the RV compliance worsens from the chronic volume overload, the RA pressure may rise and the degree of left-to-right shunting may decrease over time. Eventually, if the RA pressure exceeds the LA, the shunt may reverse and be primarily right-to-left. When this happens, systemic cyanosis appears. The major factor in the direction of shunt flow is thus the compliance of the respective atrial chambers.

The pulmonary pressures are modestly elevated in most patients with an ASD due to the high pulmonary blood flow, but severe pulmonary hypertension with cyanosis (**Eisenmenger physiology**) is actually unusual, occurring in only about 15% of the patients with an ASD alone. Increased pulmonary vascular resistance (PVR) and pulmonary hypertension secondary to pulmonary vascular disease rarely occur in childhood or young adult life in secundum defects and are more common in primum defects, especially if there is an associated VSD. Eventual RV failure may occur with any atrial shunt of significant size, and most shunts should be corrected unless they are quite small (less than 1.5:1 left-to-right shunt). In adults, a large left-to-right shunt may have begun to reverse, so the absolute left-to-right shunt measurement (Qp/Qs, where Qp = pulmonary flow and Qs = systemic flow) at the time the patient is studied may underestimate the original shunt size. In addition, in most people the LV and LA compliance normally declines more over time than the RV and RA compliance; for this reason, the natural history of small atrial septal shunts is to increase the left-to-right shunting as the patient ages. There is generally only trivial shunting with a PFO compared to a true ASD. ASDs predispose to atrial fibrillation due to RA enlargement, and paradoxical right-to-left emboli do occur. If pulmonary hypertension does occur, the 2018 guidelines recommend that the shunt should still be closed as long as the left-to-right shunt is still greater than 1.5:1 and the systolic PA pressure is less than one-half the systemic arterial pressure and the PVR calculation is less than one-third systemic vascular resistance.

Interestingly, paradoxical emboli may be more common in patients with a PFO than a true ASD, especially when there is an atrial septal aneurysm. An aneurysm of the atrial septum is not a true aneurysm but rather simply a redundancy of the atrial septum that causes it to swing back and forth (greater than 10 mm). When present with a PFO, the back-and-forth swinging tends to pull open the PFO, encouraging shunting. This may help explain why more right-to-left shunting occurs in patients with an atrial septal aneurysm and PFO than in those with a PFO alone. This creates the anatomic substrate for the occurrence of paradoxical emboli. Other factors may distort the atrial septum (such as an enlarged aorta) and result in an increased

shunting in patients with a PFO. Right-to-left PFO shunting may be more prominent upright than supine, creating orthostatic hypoxemia **(platypnea orthodeoxia).** There may also be increased shunting in patients with a PFO and sleep apnea as the RA compliance may worsen during apneic spells when pulmonary pressures increase.

Clinical Findings

A. Symptoms and Signs

Patients with a small or moderate ASD or with a PFO are asymptomatic unless a complication occurs. There is only trivial shunting in a PFO unless the RA pressure increases for some other reason or the atrial septum is distorted. With larger ASD shunts, exertional dyspnea or heart failure may develop, most commonly in the fourth decade of life or later. Prominent RV and PA pulsations are then readily visible and palpable. A moderately loud systolic ejection murmur can be heard in the second and third interspaces parasternally as a result of increased flow through the pulmonary valve. S_2 is widely split and does not vary with respiration. The left-to-right shunt across the defect decreases with inspiration (as the RA pressure increases) and then increases with expiration (as the RA pressure decreases), thus keeping the RV stroke volume relatively constant in inspiration and expiration. A **"fixed" splitting** of the second sound results. In very large left-to-right shunts, a tricuspid rumble may be heard due to the high flow across the tricuspid valve in diastole.

B. ECG and Chest Radiography

Right axis deviation or RVH may be present depending on the size of the RV volume overload. Incomplete or complete right bundle branch block is present in nearly all cases of ASD, and superior axis deviation (left anterior fascicular block) is noted in the complete AV septal defect, where complete heart block is often seen as well. With sinus venosus defects, the P axis is leftward of +15° due to abnormal atrial activation with loss of the upper RA tissue from around the sinus node. This creates the negative P waves in the inferior leads. The chest radiograph shows large pulmonary arteries, increased pulmonary vascularity, and an enlarged RA and RV as with all pre-tricuspid valve cardiac left-to-right shunts. The LA is not traditionally enlarged due to an ASD shunt because the chamber is being decompressed.

C. Diagnostic Studies

Echocardiography demonstrates evidence of RA and RV volume overload. The atrial defect is usually observed by echocardiography, although sinus venosus defects may be elusive since they are high in the atrial septum. Many patients with a PFO also have an atrial septal aneurysm (defined as greater than 10-mm excursion of the septum from the static position). Echocardiography with saline injection **(bubble contrast)** can demonstrate the right-to-left component of the shunt, and both pulsed and color flow Doppler flow studies can demonstrate shunting in either direction. In platypnea orthodeoxia, the shunt may primarily result from inferior vena cava blood, and a femoral vein saline injection may be required to demonstrate the shunt. Transesophageal echocardiography (TEE) is helpful when transthoracic echocardiography quality is not optimal because it improves the sensitivity for detection of small shunts and provides a better assessment of PFO or ASD anatomy. Both CT and MRI can elucidate the atrial septal anatomy, better detect multiple fenestrations, and demonstrate associated lesions such as anomalous pulmonary venous connections. Atrial septal anatomy can be complex, and either MRI, TEE, or CT can reveal whether there is an adequate rim around the defect to allow for safe positioning of an atrial septal occluder device. These studies can also help identify any anomalous pulmonary venous connections. Cardiac catheterization can define the size and location of the shunt and determine the pulmonary pressure and PVR.

Prognosis & Treatment

Patients with small atrial shunts live a normal life span with no intervention. Large shunts usually cause disability by age 40 years. Because left-to-right shunts and RV overload tend to increase with normal age-related reduction in LV (and subsequently LA) compliance, both AHA/ACC and the ESC guidelines suggest that closure of all left-to-right shunts greater than 1.5:1 should be accomplished either by a percutaneous device or by surgery if any right heart structures are enlarged at all. If the pulmonary systolic pressure is more than two-thirds the systemic systolic pressure, then pulmonary hypertension may preclude ASD closure. The ESC guidelines add the pulmonary vascular resistance to the criteria and consider it a class IIa indication if the PVR is between 3 and 5 Wood units, and the guidelines preclude the use of closure if the PVR is greater than or equal to 5 Wood units. Testing with transient balloon occlusion of the shunt, with pulmonary vasodilators, or with both may be required in the presence of pulmonary hypertension. Preservation of the cardiac output after transient balloon occlusion and evidence for preserved pulmonary vasoreactivity with pulmonary vasodilator testing all favor closure when pulmonary hypertension and at least a 1.5:1 left-to-right shunt are present. ESC guidelines favor bringing the patient back to the catheterization laboratory for retesting on pulmonary vasodilators, rather than using acute testing, to see if the PVR can be reduced below 5 Wood units. The ESC guidelines also suggest considering fenestrated closure in the face of pulmonary hypertension. The use of bosentan or sildenafil is recommended if the PVR is over 5 Wood units and there is a right-to-left shunt. After age 40 years, cardiac arrhythmias (especially atrial fibrillation) and heart failure occur with increased frequency due to the chronic right heart volume overload. Paradoxical systemic arterial embolization also becomes more of a concern as RV compliance is lost and the left-to-right shunt begins to reverse.

PFOs are usually *not* associated with significant shunting, and therefore, the patients are hemodynamically asymptomatic and the heart size is normal. However, PFOs can be responsible for paradoxical emboli and are a possible cause of **cryptogenic strokes** in patients

under age 55 years. Some shunting may occur with exercise if the right heart is enlarged or stiff. *Interestingly, the risk of recurrent paradoxical emboli is low regardless of whether the PFO is closed or not, and that observation has reduced the value of closing these defects in cryptogenic stroke.* Further confounding the advantage of PFO closure for cryptogenic stroke or transient ischemic attack (TIA) has been the discovery of frequent bouts of paroxysmal atrial fibrillation using 30-day monitoring in these patients, suggesting atrial fibrillation is actually the real stroke/TIA risk factor in some patients.

Occasionally, a PFO that has not been pathologic may become responsible for cyanosis, especially if the RA pressure is elevated from pulmonary or RV hypertension or from severe tricuspid regurgitation.

Surgery involves stitching or patching of the foramen. For ostium secundum ASDs, percutaneous closure by use of a variety of devices is preferred over surgery when the anatomy is appropriate (usually this means there must be an adequate atrial septal rim around the defect to secure the occluder device).

Patients who have hypoxemia (especially upon standing or with exercise) should have the PFO closed if no other cause for hypoxemia is evident and there is right-to-left shunting demonstrated through the PFO. For patients with cryptogenic stroke or TIA, it remains uncertain whether closure of the PFO, either by open surgical or percutaneous techniques, has any advantage over anticoagulation with either warfarin, a DOAC, or aspirin.

From a practical standpoint, **patients younger than 55 years with cryptogenic stroke/TIA and no other identifiable cause except for the presence of a PFO should still be considered for PFO closure**. A 2020 update from the guideline subcommittee of the American Academy of Neurology reaffirms no change in this overall policy. The presence of an atrial septal aneurysm (with the septum appearing "floppy" on echocardiogram) has been associated with a higher risk of recurrent stroke/TIA in patients with cryptogenic stroke/TIA. A workup for any causes for hypercoagulability and a 30-day monitor should be part of the clinical assessment to exclude other potential causes for cryptogenic stroke/TIA. In meta-analysis of data in patients with cryptogenic stroke/TIA and PFO who have their PFO closed, ischemic stroke recurrence is less frequent compared with patients receiving medical treatment. Atrial fibrillation is more frequent but mostly transient in patients who have device closure. There is no difference in TIA, all-cause mortality, or MI between those treated with medicine versus a closure device. In a large, multicenter trial in France among patients who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone. PFO closure was associated with an increased risk of atrial fibrillation. Residual shunting after device closure is also present in up to 25% of patients. A report from Massachusetts General Hospital found a medium to large residual shunt increased the risk of a recurrent stroke or TIA threefold.

When to Refer

- All patients with an ASD should be evaluated by a cardiologist with expertise in adult congenital disease to ensure no other structural disease is present and to investigate whether the RV is enlarged.
- If the RA and RV sizes remain normal, serial echocardiography should be performed every 3–5 years.
- If the RA and RV volumes are increased, then referral to a cardiologist who performs percutaneous closure is warranted.
- Patients younger than 55 years with cryptogenic stroke when no other source is identified except for a PFO with right-to-left shunting should be considered for PFO closure or medical therapy. An associated atrial septal aneurysm or evidence for hypercoagulability increases risk. Aspirin alone appears not to be effective. DOACs with or without device closure of the PFO may have a role in preventing recurrent stroke.
- Patients with cyanosis and a PFO with evidence of a right-to-left shunt by agitated saline bubble contrast on echocardiography, especially if the cyanosis is worsened upon assuming the upright posture.

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Turc G et al. Atrial septal aneurysm, shunt size and recurrent stroke risk in patients with a PFO. J Am Coll Cardiol. 2020;75:2312. [PMID: 32381162]

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VENTRICULAR SEPTAL DEFECT

ESSENTIALS OF DIAGNOSIS

- A restrictive VSD is small and makes a louder murmur than an unrestricted one, often with an accompanying thrill. The higher the gradient across the septum, the smaller the left-to-right shunt.
- Small defects may be asymptomatic.
- Larger defects result in pulmonary hypertension (Eisenmenger physiology) if not repaired or if the pulmonary circuit is not protected by RV outflow tract obstruction.
- Echocardiography/Doppler is diagnostic.

General Considerations

Congenital VSDs occur in various parts of the ventricular septum. Membranous and muscular septal defects may spontaneously close in childhood as the septum grows and hypertrophies. A left-to-right shunt is present, with the degree depending on associated systolic RV pressure. The smaller the defect, the greater is the gradient from the LV to the RV and the louder the murmur. The presentation in adults depends on the size of the shunt and whether there is associated pulmonic or subpulmonic stenosis that has protected the lung from the systemic pressure and volume. Unprotected lungs with large shunts invariably lead to pulmonary vascular disease and severe pulmonary hypertension (Eisenmenger physiology). VSD sizes are defined by comparison to the aortic root size; a small or restrictive VSD diameter is less than 25% of the aortic root diameter, a moderately restrictive VSD diameter is 25–75% of the aorta, and an unrestricted VSD size is greater than 75% of the aortic diameter. The size can also be quantitated based on the Qp/Qs (left-to-right shunt), with a restrictive lesion being less than 1.5:1, moderately restrictive VSD being 1.5–2.2:1, and an unrestricted lesion being greater than 2.2:1.

Clinical Findings

A. Symptoms and Signs

The clinical features depend on the size of the defect and the presence or absence of RV outflow obstruction or increased PVR. Small shunts are associated with loud, harsh holosystolic murmurs in the left third and fourth interspaces along the sternum. A systolic thrill is common. Larger shunts may create both LV and RV volume and pressure overload. If pulmonary hypertension occurs, high-pressure pulmonary valve regurgitation may result. Right heart failure may gradually become evident late in the course, and the shunt will begin to balance or reverse as RV and LV systolic pressures equalize with the advent of pulmonary hypertension. Cyanosis from a developing right-to-left shunt may then occur. Cyanosis with pulmonary hypertension and an intracardiac shunt define the **Eisenmenger syndrome.**

B. ECG and Chest Radiography

The ECG may be normal or may show right, left, or biventricular hypertrophy, depending on the size of the defect and the PVR. With large shunts, the LV, the LA, and the pulmonary arteries are enlarged and pulmonary vascularity is increased on chest radiographs. The RV is often normal until late in the process. If an increased PVR (pulmonary hypertension) evolves, an enlarged PA with pruning of the distal pulmonary vascular bed is seen. In rare cases of a VSD high in the ventricular septum, an aortic cusp (right coronary cusp) may prolapse into the VSD and reduce the VSD shunt but result in acute aortic regurgitation and acute heart failure.

C. Diagnostic Studies

Echocardiography can demonstrate the size of the overloaded chambers and can usually define the defect anatomy. Doppler can qualitatively assess the magnitude of shunting by noting the gradient from LV to RV and, if some tricuspid regurgitation is present, the RV systolic pressure can be estimated. The septal leaflet of the tricuspid valve may be part of the VSD anatomy and the complex appears as a ventricular septal "aneurysm." These membranous septal aneurysms resemble a "windsock" and may fenestrate and result in a VSD shunt being present or they may remain intact. Color flow Doppler helps delineate the shunt severity and the presence of valvular regurgitation. MRI and cardiac CT can often visualize the defect and describe any other anatomic abnormalities. MRI can provide quantitative shunt data as well.

Cardiac catheterization is usually reserved for those with at least moderate shunting, to quantitate the PVR and the degree of pulmonary hypertension. The 2018 adult congenital heart disease guidelines suggest that if there is still at least a 1.5:1 left-to-right shunt and if the PVR is less than one-third that of the systemic vascular resistance, and the PA systolic pressure is more than one-half of the aortic systolic pressure, then the risk of VSD closure despite some pulmonary hypertension is acceptable and it should be done. If the PVR/systemic vascular resistance ratio or the systolic PA pressure/systolic aortic pressure ratio is greater than two-thirds or there is a net right-to-left shunt, then closure is contraindicated.

The vasoreactivity of the pulmonary circuit may be tested at catheterization using agents such as inhaled nitric oxide. The AHA/ACC guidelines suggest that if the pulmonary pressures can be lowered enough and the above ratios fall below the two-thirds value, then repair is reasonable as long as the left-to-right VSD shunt is greater than 1.5:1. The 2020 ESC guidelines focus not on the pulmonary to systemic systolic BP ratio, but on the pulmonary pressure and the PVR. A PVR of greater than or equal to 5 Wood units is considered inoperable unless pulmonary vasodilators can reduce the PVR to below that value. Bosentan, an endothelial receptor blocker that reduces pulmonary pressure in Eisenmenger syndrome, has been given a class I indication in these patients in both guidelines.

Prognosis & Treatment

Patients with a small VSD have a normal life expectancy except for the small risk of infective endocarditis. Antibiotic prophylaxis after dental work is recommended only when the VSD is residual from a prior patch closure or when there is associated pulmonary hypertension and cyanosis (see Tables 33–3, 33–4, and 33–5). With large VSD shunts, heart failure may develop early in life, and survival beyond age 40 years is unusual without intervention.

Small shunts (pulmonary-to-systemic flow ratio less than 1.5) in asymptomatic patients do not require surgery or other intervention. The presence of RV infundibular stenosis or pulmonary valve stenosis may protect the pulmonary circuit such that some patients, even with a large VSD, may still be surgical candidates as adults if there is no pulmonary hypertension.

Surgical repair of a VSD is generally a low-risk procedure unless there is significant Eisenmenger physiology. Devices for nonsurgical closure of muscular VSDs are

approved and those for membranous VSDs are being implanted with promising results; however, conduction disturbance is a major complication. The percutaneous devices are also approved for closure of a VSD related to acute MI, although the results in this very high-risk patient population have not been encouraging. In the acute MI setting, the devices have also been put across the ventricular septum at surgery to help provide a firm base on which to sew a pericardial patch, given the VSD in acute MI is often associated with widespread necrosis and multiple, serpiginous pathways. A percutaneous method, wherein the two sides of the device are sewn together using a subxiphoid approach, has been described. The medications used to treat pulmonary hypertension secondary to a VSD are similar to those used to treat idiopathic ("primary") pulmonary hypertension and at times can be quite effective in relieving symptoms and reducing the degree of cyanosis. **All patients who have a right-to-left shunt present should have filters placed on any intravenous lines to avoid any contamination or air bubbles from becoming systemic.**

When to Refer

All patients with a VSD should be referred to a cardiologist with expertise in adult congenital disease to decide if long-term follow-up or further studies are warranted.

Hong ZN et al. A meta-analysis of perventricular device closure of perimembranous ventricular septal defect. J Cardiothorac Surg. 2019;14:119. [PMID: 31248430]
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TETRALOGY OF FALLOT

ESSENTIALS OF DIAGNOSIS

- Five features are characteristic:
  - VSD.
  - Concentric RVH.
  - RV outflow obstruction due to infundibular stenosis.
  - Septal overriding of the aorta in half the patients.
  - A right-sided aortic arch in 25%.
- Most adult patients with tetralogy of Fallot have been operated on, usually with an RV outflow patch and VSD closure. If patch overrides the pulmonary valve annulus, pulmonary regurgitation is common.
- Physical examination may be deceptive after classic tetralogy repair, with severe pulmonary valve regurgitation difficult to detect.
- Echocardiography/Doppler may underestimate significant pulmonary valve regurgitation. Be wary if the RV is enlarged or enlarging.
- Arrhythmias are common; periodic ambulatory monitoring is recommended.
- Serious arrhythmias and sudden death may occur if the QRS is wide or the RV becomes quite large, or both.

General Considerations

Patients with tetralogy of Fallot have a VSD, RV infundibular stenosis, RVH, and a dilated aorta (in about half of patients it overrides the septum). If there is an associated ASD, the complex is referred to as pentalogy of Fallot. The basic lesion is a large VSD with migration of the septum above the VSD and under the pulmonary valve. There may be pulmonary valve stenosis as well, usually due to either a bicuspid pulmonary valve or RV outflow hypoplasia. The aorta can be quite enlarged and aortic regurgitation may occur. If more than 50% of the aorta overrides the ventricular septum, it is called **double outlet RV**. Two vascular abnormalities are common: a right-sided aortic arch (in 25%) and an anomalous left anterior descending coronary artery from the right cusp (7–9%). The latter is important in that surgical correction must avoid injuring the coronary artery when repairing the RV outflow obstruction. Pulmonary branch stenosis may also be present.

Most adult patients have undergone prior surgery. If significant RV outflow obstruction is present in the neonatal period, a systemic arterial to pulmonary artery shunt may be the initial surgical procedure to improve pulmonary blood flow, though many infants undergo repair without this first step. Most adults will have had this initial palliative repair, however. The palliative procedure enables blood to reach the underperfused lung either by directly attaching one of the subclavian arteries to a main PA branch (**classic Blalock shunt**) or, more likely, by creating a conduit between the two (**modified Blalock shunt**). Total repair of the tetralogy of Fallot generally includes a VSD patch and usually an enlarging RV outflow tract patch, as well as a take-down of any prior arterial-pulmonary artery shunt. If the RV outflow tract patch extends through the pulmonary valve into the PA (transannular patch), varying degrees of pulmonary valve regurgitation develop. Most surgeons approach the inside of the RV via the right atrium and through the tricuspid valve and try to avoid a transannular patch if possible. Over the years, the volume overload from residual severe pulmonary valve regurgitation becomes the major hemodynamic problem to deal with in adults. A large RV outflow patch contributes to a relative RV volume load. Ventricular arrhythmias can originate from the edge of either the VSD or outflow tract patch and tend to increase in frequency as the size of the RV increases.

Clinical Findings

Most adult patients in whom tetralogy of Fallot has been repaired are relatively asymptomatic unless right heart failure occurs or arrhythmias become an issue. Patients can be active and generally require no specific therapy.

A. Symptoms and Signs

Physical examination should include checking both arms for any loss of pulse from a prior shunt procedure in infancy. The jugular venous pulsations (JVP) may reveal an increased *a* wave from poor RV compliance or rarely a *c-v* wave due to tricuspid regurgitation. The right-sided arch has no consequence. The precordium may be active, often with a persistent pulmonary outflow murmur. P_2 may or may not be audible. A right-sided gallop may be heard. A residual VSD or an aortic regurgitation murmur may be present.

B. ECG and Chest Radiography

The ECG reveals RVH and right axis deviation; in repaired tetralogy, there is often a right bundle branch block pattern. The chest radiograph shows a classic boot-shaped heart with prominence of the RV and a concavity in the RV outflow tract. This may be less impressive following repair. The aorta may be enlarged and right sided. **Importantly, the width of the QRS should be examined yearly because a QRS width of more than 180 msec is one of the risks for sudden death, although newer data suggest that this cutoff is not as specific as once thought.** Most experts recommend ambulatory monitoring periodically as well, especially if the patient experiences palpitations. Other identified risk factors for ventricular arrhythmias include having multiple prior cardiac surgeries, an elevated LV end-diastolic pressure (LVEDP), and older age at time of repair. In fact, it appears that the more the left side of the heart is involved, the higher the risk of sudden death.

C. Diagnostic Studies

Echocardiography/Doppler usually establishes the diagnosis by noting the unrestricted (large) VSD, the RV infundibular stenosis, and the enlarged aorta. In patients who have had tetralogy of Fallot repaired, echocardiography/Doppler also provides data regarding the amount of residual pulmonary valve regurgitation if a transannular patch is present, RV and LV function, and the presence of aortic regurgitation. Elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) blood levels have also been correlated with increasing RV enlargement.

Cardiac MRI and CT can quantitate both the pulmonary regurgitation and the RV volumes. In addition, cardiac MRI and CT can identify whether there is either a native pulmonary arterial branch stenosis or a stenosis at the distal site of a prior arterial-to-PA shunt or other anomalies, such as an ASD. The ability of cardiac MRI to accurately quantitate the pulmonary regurgitation severity and provide more accurate RV volume measurements gives it an advantage over other imaging studies. Cardiac catheterization may be required to document the degree of pulmonary valve regurgitation because noninvasive studies depend on velocity gradients. Pulmonary angiography demonstrates the degree of pulmonary valve regurgitation, and RV angiography helps assess any postoperative outflow tract aneurysm.

The need for electrophysiologic studies with ventricular stimulation and potential ventricular tachycardia ablation has been suggested by some experts for patients who have had evidence for ventricular tachycardia, unexplained syncope, a wide QRS, are older, or who are about to undergo pulmonary valve replacement.

Prognosis & Treatment

A few patients with "just the right amount" of subpulmonic stenosis enter adulthood without having had surgical correction. However, most adult patients have had surgical repair, including VSD closure, resection of infundibular muscle, and insertion of an outflow tract patch to relieve the subpulmonic obstruction. Patients with pulmonary valve regurgitation should be monitored to ensure the RV volume does not progressively increase. In patients with tetralogy of Fallot, transthoracic echocardiogram monitoring of pulmonary valve regurgitation is recommended every 12–24 months based on the degree of regurgitation. Low-pressure pulmonary valve regurgitation is difficult to diagnose due to the fact that the RV diastolic pressures tend to be high and the pulmonary arterial diastolic pressure low. This means there is little gradient between the PA and the RV in diastole, so that there may be little murmur or evidence of turbulence on color flow Doppler. If the RV begins to enlarge, it must be assumed that this is due to pulmonary valve regurgitation until proven otherwise. Early surgical pulmonary valve replacement is increasingly being favored. The RV volumes from cardiac MRI are important in deciding when to intervene if the patient is not very symptomatic; an RV end-diastolic volume index of greater than 160 mm/m^2 or an RV end-systolic volume index of greater than 80 mm/m^2 is recommended as the cutoff. There are also a number of other triggers for intervention, details of which can be found in the AHA/ACC and ESC guidelines. A percutaneous approach to pulmonary valve regurgitation remains limited as the available percutaneous valve diameters are frequently too small for the size of the pulmonary annulus. The Melody valve is a bovine jugular vein prosthesis with the largest size being 22 mm in diameter. Percutaneous stented valves, particularly the Edwards SAPIEN XT, have been used successfully and can be used in patients with larger pulmonary root sizes. Often, a regular stent is placed within the PA first, with the stented valve then placed within this first stent. The expansion of the PA must not impede flow down any coronary artery; this is tested by a trial balloon expansion while imaging the coronary artery at the same time (class I requirement). There has been an increase in stented valve endocarditis noted after the placement of the Melody valve; this is being closely monitored.

If an anomalous coronary artery is present, then an extracardiac conduit around it from the RV to the PA may be necessary as part of the tetralogy repair. By 20-year follow-up, reoperation of the common tetralogy repair is needed in about 10–15%, not only for severe pulmonary valve regurgitation but also for residual infundibular stenosis. Usually the pulmonary valve is replaced with a pulmonary homograft, although a porcine bioprosthetic valve is also suitable. Percutaneous valve-in-valve stented bioprosthetic valves have successfully been used when there is surgical bioprosthetic valve dysfunction. Cryoablation of the tissue giving rise to arrhythmias is sometimes

performed at the time of reoperation. Branch pulmonary stenosis may be percutaneously opened by stenting. If a conduit has been used already for repair of the RV outflow obstruction, a percutaneous approach with a stented pulmonary valve may be possible. All patients require endocarditis prophylaxis (see Tables 33–3, 33–4, and 33–5). Most adults with stable hemodynamics can be quite active, and most women can carry a pregnancy adequately if RV function is preserved.

Atrial fibrillation, reentrant atrial arrhythmias, and ventricular ectopy are common, especially after the age of 45. Left heart disease appears to cause arrhythmias more often than right heart disease. Biventricular dysfunction is not an uncommon consequence as the patient ages. The cause of associated LV dysfunction is often multifactorial and frequently unclear. Similarly, the aorta may enlarge with accompanying aortic regurgitation, and these lesions can become severe enough to warrant surgical intervention. Patients with RV or LV dysfunction or with dysfunction of both ventricles may require a prophylactic defibrillator.

When to Refer

All patients with tetralogy of Fallot should be referred to a cardiologist with expertise in adult congenital heart disease.

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VALVULAR HEART DISEASE

The typical findings of each native valve lesion are described in Table 10–1. Table 10–2 outlines bedside maneuvers to distinguish among the various systolic murmurs.

The 2017 ACC/AHA valvular heart disease guidelines suggest all lesions may be best classified clinically into one of six categories based on anatomy and symptoms.

Stage A: Patients at risk for valvular heart disease.

Stage B: Patients with progressive valvular heart disease (mild to moderate severity) and asymptomatic.

Stage C: Asymptomatic patients who have reached criteria for severe valvular heart disease.

C1: Severe valve lesion. Asymptomatic. Normal LV function.

C2: Severe valve lesion. Asymptomatic. Abnormal LV function.

Stage D: Symptomatic patients as a result of valvular heart disease.

In 2020, the ACC/AHA guideline for the management of patients with valvular heart disease was published and this chapter will highlight the changes and additions from the prior guidelines, first published in 2014 and then updated in 2017.

Nishimura RA et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2017;135:e1159. [PMID: 28298458]
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MITRAL STENOSIS

ESSENTIALS OF DIAGNOSIS

- Fatigue, exertional dyspnea, and orthopnea when the stenosis becomes severe.
- Symptoms often precipitated by onset of atrial fibrillation or pregnancy.
- Intervention indicated for symptoms, atrial fibrillation, or evidence of pulmonary hypertension. Most symptomatic patients have a mitral valve area of < 1.5 cm^2.

General Considerations

Most patients with native valve mitral stenosis are presumed to have had rheumatic heart disease, although a history of rheumatic fever is noted in only about one-third. (Also see section on Rheumatic Fever.) Rheumatic mitral stenosis results in thickening of the leaflets, fusion of the mitral commissures, retraction, thickening and fusion of the chordae, and calcium deposition in the valve. Mitral stenosis can also occur due to congenital disease with chordal fusion or papillary muscle malposition. The papillary muscles may be abnormally close together, sometimes so close that they merge into a single papillary muscle (the **"parachute mitral valve"**). In these patients, the chordae or valvular tissue (or both) may also be fused. In older patients and in those undergoing dialysis, mitral annular calcification may stiffen the mitral valve and reduce its motion to the point where a mitral gradient is present. Calcium in the mitral annulus virtually invades the mitral leaflet from the annulus inward as opposed to the calcium buildup in the leaflets and commissures as seen in rheumatic heart disease. Mitral valve obstruction may also develop in patients who have had mitral valve repair with a mitral annular ring that is too small, or in patients who have had a surgical valve replacement (prosthetic valve-patient mismatch or degeneration of the prosthetic valve over time).

Table 10–1. Differential diagnosis of valvular heart disease.

	Mitral Stenosis	Mitral Regurgitation	Aortic Stenosis	Aortic Regurgitation	Tricuspid Stenosis	Tricuspid Regurgitation
Inspection	Malar flush, precordial bulge, and diffuse pulsation in young patients.	Usually prominent and hyperdynamic apical impulse to left of MCL.	Sustained PMI, prominent atrial filling wave.	Hyperdynamic PMI to left of MCL and downward. Visible carotid pulsations. Pulsating nailbeds (Quincke sign), head bob (deMusset sign).	Giant *a* wave in jugular pulse with sinus rhythm. Peripheral edema or ascites, or both.	Large *v* wave in jugular pulse; time with carotid pulsation. Peripheral edema or ascites, or both.
Palpation	"Tapping" sensation over area of expected PMI. Right ventricular pulsation in left third to fifth ICS parasternally when pulmonary hypertension is present. P_2 may be palpable.	Forceful, brisk PMI; systolic thrill over PMI. Pulse normal, small, or slightly collapsing.	Powerful, heaving PMI to left and slightly below MCL. Systolic thrill over aortic area, sternal notch, or carotid arteries in severe disease. Small and slowly rising carotid pulse. If bicuspid AS, check for delay at femoral artery to exclude coarctation.	Apical impulse forceful and displaced significantly to left and downward. Prominent carotid pulses. Rapidly rising and collapsing pulses (Corrigan pulse).	Pulsating, enlarged liver in ventricular systole.	Right ventricular pulsation. Systolic pulsation of liver.
Heart sounds, rhythm, and blood pressure	S_1 loud if valve mobile. Opening snap following S_2. The worse the disease, the closer the S_2-opening snap interval.	S_1 normal or buried in early part of murmur (exception in mitral prolapse where murmur may be late). Prominent third heart sound when severe MR. Atrial fibrillation common. Blood pressure normal. Midsystolic clicks may be present and may be multiple.	A_2 normal, soft, or absent. Prominent S_4. Blood pressure normal, or systolic pressure normal with high diastolic pressure.	S_1 normal or reduced, A_2 loud. Wide pulse pressure with diastolic pressure < 60 mm Hg. When severe, gentle compression of femoral artery with diaphragm of stethoscope may reveal diastolic flow (Duroziez) and pressure in leg on palpation > 40 mm Hg than in arm (Hill).	S_1 often loud.	Atrial fibrillation may be present.
Murmurs						
Location and transmission	Localized at or near apex. Diastolic rumble best heard in left lateral position; may be accentuated by having patient do sit-ups. Rarely, short diastolic murmur along lower left sternal border (Graham Steell) in severe pulmonary hypertension.	Loudest over PMI; posteriorly directed jets (ie, anterior mitral prolapse) transmitted to left axilla, left infrascapular area; anteriorly directed jets (ie, posterior mitral prolapse) heard over anterior precordium. Murmur unchanged after premature beat.	Right second ICS parasternally or at apex, heard in carotid arteries and occasionally in upper interscapular area. May sound like MR at apex (Gallaverdin phenomenon), but murmur occurs after S_1 and stops before S_2.	Diastolic: louder along left sternal border in third to fourth interspace. Heard over aortic area and apex. May be associated with low-pitched mid-diastolic murmur at apex (Austin Flint) due to functional mitral stenosis. If due to an enlarged aorta, murmur may radiate to right sternal border.	Third to fifth ICS along left sternal border out to apex. Murmur increases with inspiration.	Third to fifth ICS along left sternal border. Murmur hard to hear but increases with inspiration. Sit-ups can increase cardiac output and accentuate murmur.

(*continued*)

Table 10–1. Differential diagnosis of valvular heart disease. (continued)

	Mitral Stenosis	Mitral Regurgitation	Aortic Stenosis	Aortic Regurgitation	Tricuspid Stenosis	Tricuspid Regurgitation
Timing	Relation of opening snap to A_2 important. The higher the LA pressure, the earlier the opening snap. Presystolic accentuation before S_1 if in sinus rhythm. Graham Steell begins with P_2 (early diastole) if associated pulmonary hypertension.	Pansystolic: begins with S_1 and ends at or after A_2. May be late systolic in mitral valve prolapse.	Begins after S_1, ends before A_2. The more severe the stenosis, the later the murmur peaks.	Begins immediately after aortic second sound and ends before first sound (blurring both); helps distinguish from MR.	Rumble often follows audible opening snap.	At times, hard to hear. Begins with S_1 and fills systole. Increases with inspiration.
Character	Low-pitched, rumbling; presystolic murmur merges with loud S_1.	Blowing, high-pitched; occasionally harsh or musical.	Harsh, rough.	Blowing, often faint.	As for mitral stenosis.	Blowing, coarse, or musical.
Optimum auscultatory conditions	After exercise, left lateral recumbency. Use stethoscope bell, lightly applied.	After exercise; use stethoscope diaphragm. In prolapse, findings may be more evident while standing.	Use stethoscope diaphragm. Patient resting, leaning forward, breath held in full expiration.	Use stethoscope diaphragm. Patient leaning forward, breath held in expiration.	Use stethoscope bell. Murmur usually louder and at peak during inspiration. Patient recumbent.	Use stethoscope diaphragm. Murmur usually becomes louder during inspiration.
Radiography	Straight left heart border from enlarged LA appendage. Elevation of left mainstem bronchus. Large right ventricle and pulmonary artery if pulmonary hypertension is present. Calcification in mitral valve in rheumatic mitral stenosis or in annulus in calcific mitral stenosis.	Enlarged LV and LA.	Concentric LVH. Prominent ascending aorta. Calcified aortic valve common.	Moderate to severe LV enlargement. Aortic root often dilated.	Enlarged right atrium with prominent SVC and azygous shadow.	Enlarged right atrium and right ventricle.
ECG	Broad P waves in standard leads; broad negative phase of diphasic P in V_1. If pulmonary hypertension is present, tall peaked P waves, right axis deviation, or right ventricular hypertrophy appears.	Left axis deviation or frank LVH. P waves broad, tall, or notched in standard leads. Broad negative phase of diphasic P in V_1.	LVH.	LVH.	Tall, peaked P waves. Possible right ventricular hypertrophy.	Right axis usual.

Echocardiography						
Two-dimensional echocardiography	Thickened, immobile mitral valve with anterior and posterior leaflets moving together. "Hockey stick" shape to opened anterior leaflet in rheumatic mitral stenosis. Annular calcium with thin leaflets in calcific mitral stenosis. LA enlargement, normal to small LV. Orifice can be traced to approximate mitral valve orifice area.	Thickened mitral valve in rheumatic disease; mitral valve prolapse; flail leaflet or vegetations may be seen. Dilated LV in volume overload. Operate for LV end-systolic dimension < 4.5 cm.	Dense persistent echoes from the aortic valve with poor leaflet excursion. LVH late in the disease. Bicuspid valve in younger patients.	Abnormal aortic valve or dilated aortic root. Diastolic vibrations of the anterior leaflet of the mitral valve and septum. In acute aortic regurgitation, premature closure of the mitral valve before the QRS. When severe, dilated LV with normal or decreased contractility. Operate when LV end-systolic dimension > 5.0 cm.	In rheumatic disease, tricuspid valve thickening, decreased early diastolic filling slope of the tricuspid valve. In carcinoid, leaflets fixed, but no significant thickening.	Enlarged right ventricle with paradoxical septal motion. Tricuspid valve often pulled open by displaced chordae.
Continuous and color flow Doppler and TEE	Prolonged pressure half-time across mitral valve allows estimation of gradient. MVA estimated from pressure half-time. Indirect evidence of pulmonary hypertension by noting elevated right ventricular systolic pressure measured from the tricuspid regurgitation jet.	Regurgitant flow mapped into LA. Use of PISA helps assess MR severity. TEE important in prosthetic mitral valve regurgitation.	Increased transvalvular flow velocity; severe AS when peak jet > 4 m/seconds (64 mm Hg). Valve area estimate using continuity equation is poorly reproducible.	Demonstrates regurgitation and qualitatively estimates severity based on percentage of LV outflow filled with jet and distance jet penetrates into LV. TEE important in aortic valve endocarditis to exclude abscess. Mitral inflow pattern describes diastolic dysfunction.	Prolonged pressure half-time across tricuspid valve can be used to estimate mean gradient. Severe tricuspid stenosis present when mean gradient > 5 mm Hg.	Regurgitant flow mapped into right atrium and venae cavae. Right ventricular systolic pressure estimated by tricuspid regurgitation jet velocity.

A_2, aortic second sound; AS, aortic stenosis; ICS, intercostal space; LA, left atrial; MCL, midclavicular line; MR, mitral regurgitation; MVA, measured valve area; P_2, pulmonary second sound; PISA, proximal isovelocity surface area; PMI, point of maximal impulse; S_1, first heart sound; S_2, second heart sound; S_4, fourth heart sound; SVC, superior vena cava; TEE, transesophageal echocardiography; V_1, chest ECG lead 1.

Table 10–2. Effect of various interventions on systolic murmurs.

Intervention	Hypertrophic Cardiomyopathy	Aortic Stenosis	Mitral Regurgitation	Mitral Prolapse
Valsalva	↑	↓	↓ or ×	↑ or ↓
Standing	↑	↑ or ×	↓ or ×	↑
Handgrip or squatting	↓	↓ or ×	↑	↓
Supine position with legs elevated	↓	↑ or ×	×	↓
Exercise	↑	↑ or ×	↓	↑

↑, increased; ↓, decreased; ×, unchanged.

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Clinical Findings

A. Symptoms and Signs

Two clinical syndromes classically occur in patients with mitral stenosis. In mild to moderate mitral stenosis, LA pressure and cardiac output may be essentially normal, and the patient is either asymptomatic or symptomatic only with extreme exertion. The measured valve area is usually between 1.5 cm^2 and 1.0 cm^2. In severe mitral stenosis (valve area less than 1.0 cm^2), severe pulmonary hypertension develops due to a "secondary stenosis" of the pulmonary vascular bed. In this condition, pulmonary edema is uncommon, but symptoms of low cardiac output and right heart failure predominate. Any measured valve area less than 1.5 cm^2 should be considered significant.

A characteristic finding of rheumatic mitral stenosis is an **opening snap** following A_2 due to the stiff mitral valve. The interval between the opening snap and aortic closure sound is long when the LA pressure is low but shortens as the LA pressure rises and approaches the aortic diastolic pressure. As mitral stenosis worsens, there is a localized low-pitched diastolic murmur whose duration increases with the severity of the stenosis as the mitral gradient continues throughout more of diastole. The diastolic murmur is best heard at the apex with the patient in the left lateral position (Table 10–1). Mitral regurgitation may be present as well.

Paroxysmal or chronic atrial fibrillation eventually develops in 50–80% of patients. Any increase in the heart rate reduces diastolic filling time and increases the mitral gradient. A sudden increase in heart rate may precipitate pulmonary edema. Therefore, heart rate control is important, with slow heart rates allowing for more diastolic filling of the LV.

B. Diagnostic Studies

Echocardiography is the most valuable technique for assessing mitral stenosis (Table 10–1). LA size can also be determined by echocardiography; increased size denotes an increased likelihood of atrial fibrillation and thrombus formation.

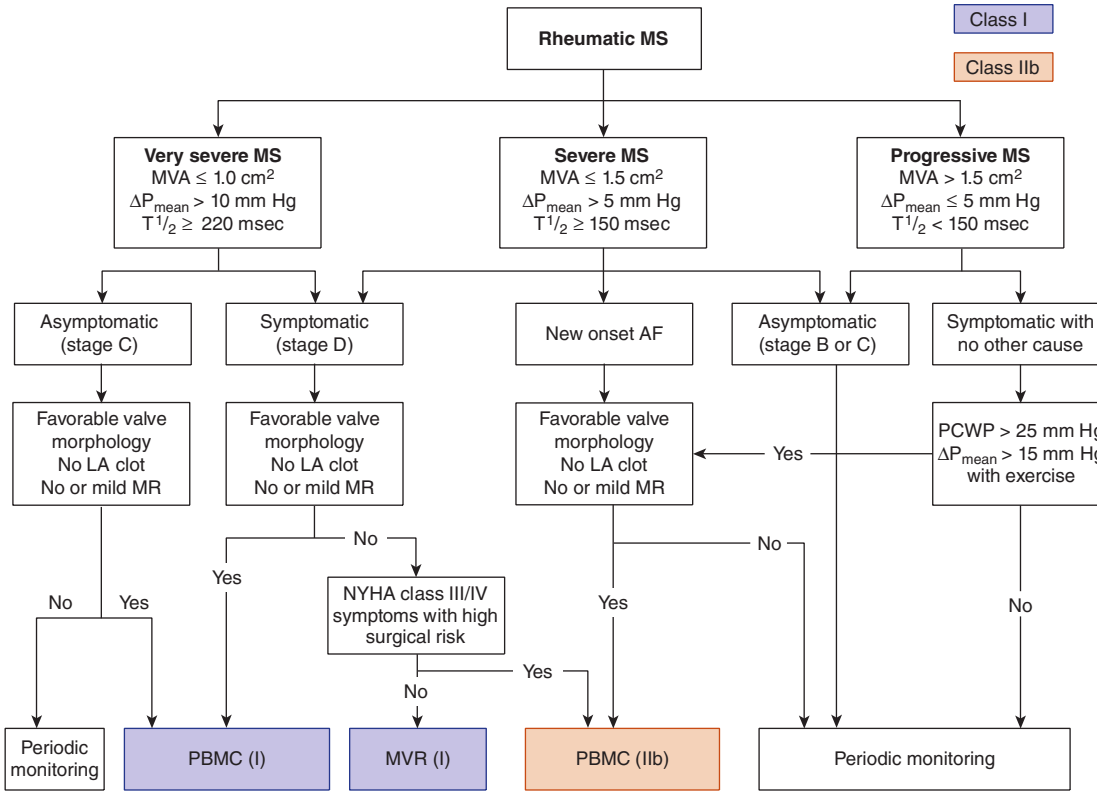
Because echocardiography and careful symptom evaluation provide most of the needed information, cardiac catheterization is used primarily to detect associated coronary or myocardial disease—usually after the decision to intervene has been made.

Treatment & Prognosis

In most cases, there is a long asymptomatic phase after the initial rheumatic infection, followed by subtle limitation of activity. Pregnancy and its associated increase in stroke volume and heart rate result in an increased transmitral pressure gradient and may precipitate symptoms. In particular, toward the end of pregnancy, the cardiac output continues to be maintained by an increase in heart rate, increasing the mitral gradient by shortening diastolic time. Patients with moderate to severe mitral stenosis should have the condition corrected prior to becoming pregnant if possible (when the measured valve area is about 2.0 cm^2). Pregnant patients who become symptomatic can undergo successful surgery, preferably in the third trimester, although balloon valvuloplasty is the treatment of choice if the echocardiography valve score is low enough.

The onset of atrial fibrillation often precipitates symptoms, which improve with control of the ventricular rate or restoration of sinus rhythm. Conversion to and subsequent maintenance of sinus rhythm are most commonly successful when the duration of atrial fibrillation is brief (less than 6–12 months) and the LA is not severely dilated (diameter less than 4.5 cm). Once atrial fibrillation occurs, the patient should receive warfarin even if sinus rhythm is restored, since atrial fibrillation often recurs even with antiarrhythmic therapy and 20–30% of these patients will have systemic embolization if untreated. Systemic embolization in the presence of only mild to moderate disease is not an indication for surgery but should be treated with warfarin. DOACs (dabigatran, apixaban, rivaroxaban, edoxaban) are *not* recommended by the most recent guidelines, since patients with atrial fibrillation were excluded from the approval trials.

Indications for intervention focus on symptoms such as an episode of pulmonary edema, a decline in exercise capacity, or any evidence of pulmonary hypertension (peak systolic pulmonary pressure greater than 50 mm Hg). Some experts believe that the presence of atrial fibrillation should also be a consideration for an intervention. Most



▲ **Figure 10–1.** The AHA/ACC guidelines for intervention in mitral stenosis. AF, atrial fibrillation; LA, left atrial; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; MVR, mitral valve replacement; NYHA, New York Heart Association; PBMC, percutaneous balloon mitral commissurotomy; PCWP, pulmonary capillary wedge pressure; ΔP_{mean}, mean pressure gradient; T½, half-life. (Reprinted with permission Circulation. 2014;129:e521–e643 ©2014 American Heart Association, Inc.)

interventions are not pursued until the patient is symptomatic (stage D) (Figure 10–1). In some patients, symptoms develop with calculated mitral valve areas between 1.5 cm^2 and 1.0 cm^2. Symptoms or evidence of pulmonary hypertension should drive the decision to intervene in these patients, not the estimated valve area.

Open mitral commissurotomy is now rarely performed and has been replaced by percutaneous balloon valvuloplasty. Ten-year follow-up data comparing surgery to balloon valvuloplasty suggest no real difference in outcome between the two modalities. Replacement of the valve is indicated when combined stenosis and regurgitation are present or when the mitral valve echo score is much greater than 8–10. To determine the valve score, numbers 1 to 4 are assigned to four valve characteristics: mobility, calcification, thickening, and submitral scar. Thus, a maximum score is 16. Percutaneous balloon valvuloplasty has a very low mortality rate (less than 0.5%) and a low morbidity rate (3–5%). Operative mortality rates are also low: 1–3% in most institutions. Repeat balloon valvuloplasty can be done if the morphology of the valve remains suitable. At surgery, a **Maze procedure** may be done at the same time to reduce recurrent atrial arrhythmias. It involves a number of endocardial incisions across the right and left atria to disrupt the electrical activity that sustains atrial arrhythmias. In many institutions, the LA appendage is sewn closed to help remove a potential future source for thrombosis.

Mechanical mitral prosthetic valves are more prone to thrombosis than mechanical aortic prosthetic valves. **The recommended INR range is thus higher (INR 2.5–3.5 or average of 3.0). Low-dose aspirin should be used in conjunction with warfarin if the bleeding risk is low.** DOACs are *not* recommended as an anticoagulant. It is a class IIa recommendation that warfarin be used for up to 6 months after implantation of a bioprosthetic mitral valve. Bioprosthetic valves tend to degenerate after about 10–15 years. Percutaneous balloon valvuloplasty is not effective when bioprosthetic valve stenosis occurs, but stented valve-in-valve procedures have been successful. However, valve-in-valve procedures are still uncommon due to the need for the technically challenging transseptal approach. Reported

early outcomes have been positive in patients with bioprosthetic valves, ring annuloplasty, and even in some calcific mitral stenosis patients. Younger patients and those with ESKD are generally believed to do the poorest with bioprosthetic heart valves, although data have questioned the role of CKD as a major risk factor. Endocarditis prophylaxis is indicated for patients with prosthetic heart valves but is not indicated in native valve disease (see Tables 33–3, 33–4, and 33–5). Mitral stenosis due to calcific encroachment of the leaflets from mitral annular calcium can progress to severe mitral stenosis at times (estimated to be about 1 in 6 over 10 years). It does not lend itself to percutaneous valvuloplasty, and there are only case reports of using a percutaneous mitral valve replacement option.

When to Refer

- Patients with mitral stenosis should be monitored with yearly examinations, and echocardiograms should be performed more frequently as the severity of the obstruction increases.
- All patients should initially be seen by a cardiologist, who can then decide how often the patient needs cardiology follow-up and whether intervention is indicated.

Kim JY et al. Outcomes of direct oral anticoagulants in patients with mitral stenosis. J Am Coll Cardiol. 2019;73:1123. [PMID: 30871695]

Tsutsui RS et al. Natural history of mitral stenosis in patients with mitral annular calcium. JACC Cardiovasc Imaging. 2019;12:1105. [PMID: 30765312]

MITRAL REGURGITATION

ESSENTIALS OF DIAGNOSIS

- May be asymptomatic for years (or for life).
- Severe mitral regurgitation may cause left-sided heart failure and lead to pulmonary hypertension and right-sided heart failure.
- For chronic primary mitral regurgitation, surgery is indicated for symptoms or when the LVEF is < 60% or the echocardiographic LV end-systolic dimension is > 4.0 cm. Surgery also indicated in patients who have a progressive increase in LV size or decline in LVEF.
- In patients with mitral prolapse and severe mitral regurgitation, earlier surgery is indicated if mitral repair can be performed successfully with a high degree of certainty.
- Transcatheter edge-to-edge repair, if possible, can be done in symptomatic patients at higher surgical risk regardless of whether the mitral regurgitation is primary or secondary.
- Patients with functional chronic mitral regurgitation may improve with biventricular pacing and guideline-directed management and therapy.

General Considerations

Mitral regurgitation results in a volume load on the heart (increases preload) and reduces afterload. The result is an enlarged LV with an increased EF. Over time, the stress of the volume overload reduces myocardial contractile function; when this occurs, there is a drop in EF and a rise in end-systolic volume.

Clinical Findings

A. Symptoms and Signs

In acute mitral regurgitation, the LA size is not large, and LA pressure rises abruptly, leading to pulmonary edema if severe. When chronic, the LA enlarges progressively and the increased volume can be handled without a major rise in the LA pressure; the pressure in pulmonary veins and capillaries may rise only during exertion. Exertional dyspnea and fatigue progress gradually over many years.

Mitral regurgitation leads to chronic LA and LV enlargement and may result in subsequent atrial fibrillation and eventually LV dysfunction. Clinically, mitral regurgitation is characterized by a pansystolic murmur maximal at the apex, radiating to the axilla and occasionally to the base. The murmur does not change in intensity after a premature beat because the LV to LA gradient is unaffected. In addition, a hyperdynamic LV impulse and a brisk carotid upstroke may be present along with a prominent third heart sound due to the increased volume returning to the LV in early diastole (Tables 10–1 and 10–2). In acute mitral regurgitation, the murmur intensity may be modest due to little difference between the LA and LV systolic pressures during ventricular systole. The mitral regurgitation murmur due to mitral valve prolapse tends to radiate anteriorly in the presence of posterior leaflet prolapse and posteriorly when the prolapse is primarily of the anterior leaflet. Mitral regurgitation may not be pansystolic in these patients but occur only after the mitral click (until late in the disease process when it then becomes progressively more holosystolic).

B. Diagnostic Studies

Echocardiographic information demonstrating the underlying pathologic process (rheumatic, calcific, prolapse, flail leaflet, endocarditis, cardiomyopathy), LV size and function, LA size, PA pressure, and RV function can be invaluable in planning treatment as well as in recognizing associated lesions. The valvular heart disease guidelines provide details of the classification and measures of severity for primary and secondary mitral valve regurgitation. Doppler techniques provide qualitative and semiquantitative estimates of the severity of mitral regurgitation. TEE may help reveal the cause of regurgitation and is especially useful in patients who have had mitral valve replacement, in suspected endocarditis, and in identifying candidates for valvular repair. Echocardiographic dimensions and measures of systolic function are critical in deciding the timing of surgery. Asymptomatic patients with severe mitral regurgitation (stage C1) but preserved LV dimensions should undergo at least yearly echocardiography. Exercise

hemodynamics with either Doppler echocardiography or cardiac catheterization may be useful when the symptoms do not fit the anatomic severity of mitral regurgitation. BNP or NT-proBNP is useful in the early identification of LV dysfunction in the presence of mitral regurgitation and asymptomatic patients, and values that trend upward over time appear to have prognostic importance.

Cardiac MRI is occasionally useful, especially if specific myocardial causes are being sought (such as amyloid or myocarditis) or if myocardial viability assessment is needed prior to deciding whether to add coronary artery bypass grafting to mitral valve surgery.

Cardiac catheterization provides a further assessment of regurgitation and its hemodynamic impact along with LV function, resting cardiac output, and PA pressure. **The guidelines recommend coronary angiography to determine the presence of incidental CAD prior to valve surgery in all men over age 40 years and in menopausal women with coronary risk factors.** In younger patients, no coronary angiography is needed unless there is a clinical suspicion of coronary disease. Cardiac multidetector coronary CT may be adequate to screen patients with valvular heart disease for asymptomatic CAD. A normal CT coronary angiogram has a high predictive value for patients with normal or insignificant disease.

Treatment & Prognosis

A. Primary Mitral Regurgitation

The degree of LV enlargement reflects the severity and chronicity of regurgitation. LV volume overload may ultimately lead to LV failure and reduced cardiac output. LA enlargement may be considerable in **chronic mitral regurgitation** and a large amount of mitral regurgitation regurgitant volume may be tolerated. Patients with chronic lesions may thus remain asymptomatic for many years. Surgery is necessary when symptoms develop or when there is evidence for LV dysfunction, since progressive and irreversible deterioration of LV function can occur prior to the onset of symptoms. Early surgery is indicated even in asymptomatic patients with a reduced EF (less than 60%) or marked LV dilation with reduced contractility (end-systolic dimension greater than 4.0 cm) (Figure 10–2).

It is a class IIa indication for mitral valve surgery when the LVEF is greater than 60% and the LV end-systolic dimension is still less than 4.0 cm but serial imaging reveals a progressive increase in the LV end-systolic dimension or a serial decrease in the EF. Pulmonary hypertension development suggests the mitral regurgitation is severe and should prompt intervention.

Acute mitral regurgitation may develop abruptly, as with papillary muscle dysfunction following MI, valve perforation in infective endocarditis, in patients with hypertrophic cardiomyopathy (HCM), or when there are ruptured chordae tendineae in patients with mitral valve prolapse. Emergency surgery may be required.

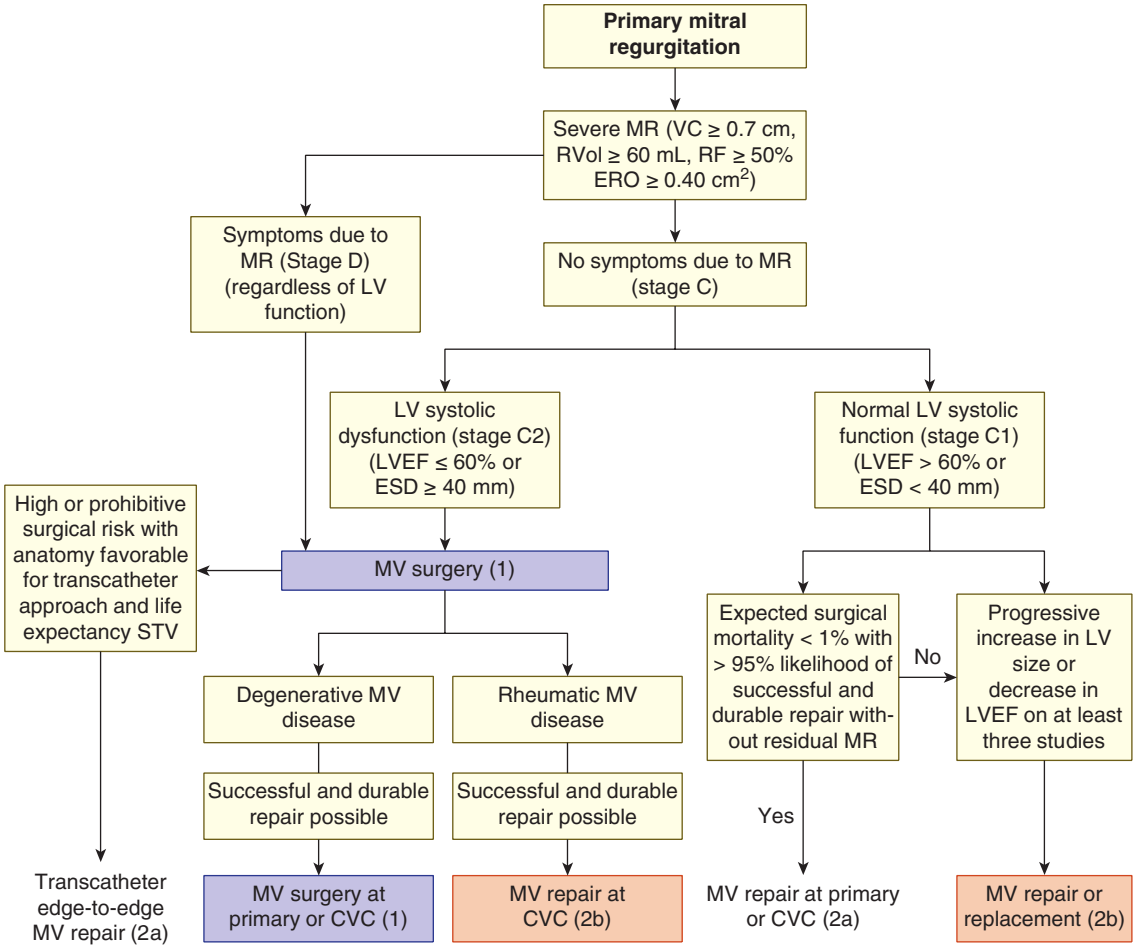
Some patients may become hemodynamically unstable and require treatment with vasodilators or intra-aortic balloon counterpulsation that reduce the amount of retrograde regurgitant flow by lowering systemic vascular resistance and improving forward stroke volume. There is controversy regarding the role of afterload reduction in chronic mitral regurgitation, since the lesion inherently results in a reduction in afterload, and there are no data that chronic afterload reduction is effective in avoiding LV dysfunction or surgical intervention. A heightened sympathetic state has led some experts to suggest that beta-blockade be considered routinely, though this also remains speculative. The mitral regurgitation in patients with tachycardia-related cardiomyopathy may improve with normalization of the heart rate.

B. Myocardial Disease and Mitral Regurgitation (Secondary Mitral Regurgitation)

When mitral regurgitation is due to cardiac dysfunction, it may subside as the infarction heals or LV dilation diminishes. The cause of the regurgitation in most of these situations is displacement of the papillary muscles and an enlarged mitral annulus rather than papillary muscle ischemia. The fundamental problem is the lack of leaflet coaptation during systole (due to either leaflet prolapse or retraction). In acute MI, rupture of the papillary muscle may occur with catastrophic results. Transient—but sometimes severe—mitral regurgitation may occur during episodes of myocardial ischemia and contribute to flash pulmonary edema. Patients with dilated cardiomyopathies of any origin may have **secondary mitral regurgitation** due to the papillary muscle displacement or dilation of the mitral annulus, or both. If mitral valve replacement is performed, preservation of the chordae to the native valve helps prevent further ventricular dilation following surgery. Initially, several groups reported good results with mitral valve repair in patients with LVEF less than 30% and secondary mitral regurgitation. Current guidelines advise that mitral valve repair/replacement can be attempted in severe mitral regurgitation patients with an EF less than 30% or an LV end-systolic dimension greater than 5.5 cm, or both, as long as repair and preservation of the chordae are possible. Figure 10–3 outlines the recommendations for intervention in secondary mitral regurgitation.

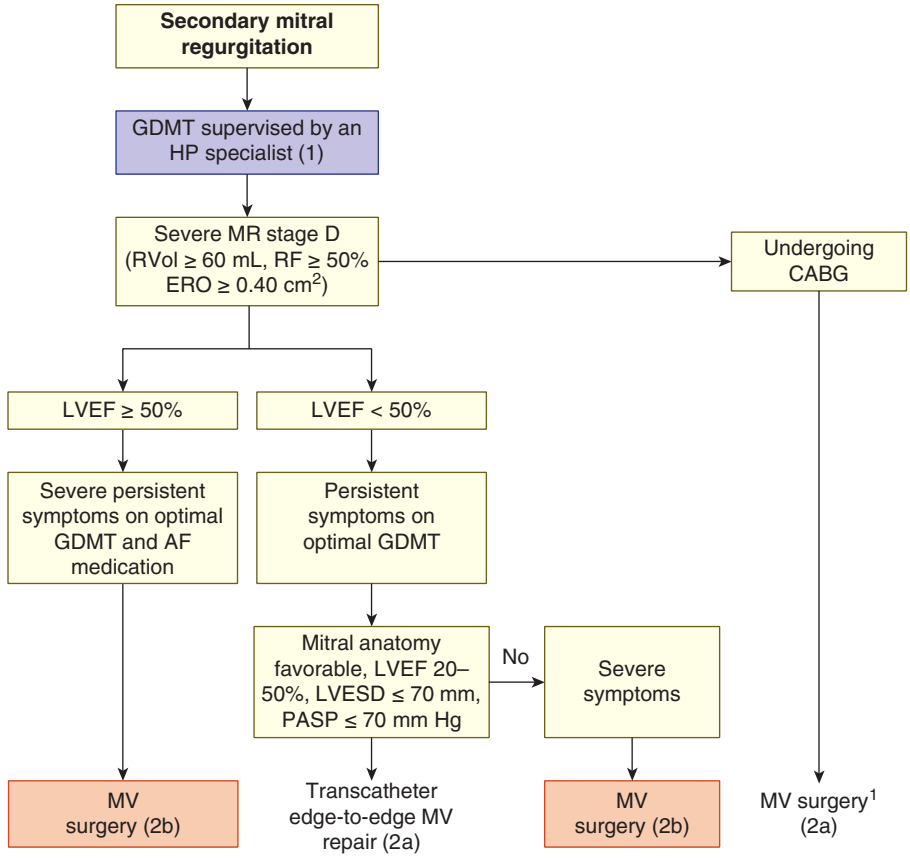
Mitral valve replacement with chordal preservation is preferred over mitral valve repair in patients with chronic ischemic cardiomyopathy. There may also be a role for cardiac resynchronization therapy with biventricular pacemaker insertion, which has been found to reduce mitral regurgitation related to cardiomyopathy in many patients. Guidelines recommend biventricular pacing prior to surgical repair in symptomatic patients who have functional mitral regurgitation as long as other criteria (eg, a QRS of greater than 150 msec or left bundle branch block or both) are present.

There are several ongoing trials of percutaneous approaches to reducing mitral regurgitation. These approaches include the use of a **mitral clip** (MitraClip) device to create a double orifice mitral valve, various coronary catheter devices to reduce the mitral annular area, and devices to reduce the septal-lateral ventricular size and consequent mitral orifice size. Of these devices, the most success has been noted with the edge-to-edge MitraClip. Two major trials have addressed the potential advantage of



▲ **Figure 10–2.** Algorithm for intervention in primary mitral regurgitation. CVC, Comprehensive valve center; ERO, effective regurgitant orifice; ESD, end-systolic dimension; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve replacement; RF, regurgitant fraction; RVol, regurgitant volume; VC, vena contracta. (Reprinted from Journal of the American College of Cardiology,77, Otto CM et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, e25–e197, 2021, with permission from Elsevier.)

the percutaneous MitraClip. In the COAPT (Clinical Outcomes Assessment of MitraClip) trial among patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximum doses of guideline-directed medical therapy, transcatheter mitral valve repair resulted in a lower rate of hospitalization for heart failure and lower all-cause mortality within 24 months of follow-up than medical therapy alone. The absolute risk reduction in all-cause mortality in patients receiving the MitraClip in the COAPT trial was 17%, which translated to a number needed to treat (NNT) of 6 to prevent 1 death over 2 years. This rather remarkably positive result, however, was tempered by another MitraClip randomized trial in a similar population that had a rather neutral result, the MITRA-FR (Percutaneous Repair with MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) study, in which the MitraClip therapy failed to show any survival benefit over medical therapy during the 1-year follow-up period. One suggestion to reconcile the differences in outcome has been suggested wherein the MitraClip is *ineffective* if the echocardiographic regurgitant orifice size is consistent with the size of the dilated LV, but the device is *effective* if the regurgitant orifice size is large compared to the size of the LV. This seemed to be verified by the results of the two trials. Current guidelines have accepted the use of the MitraClip in patients with secondary mitral regurgitation and high surgical risk. In addition, vascular plugging and occluder devices are being used in selected patients to occlude perivalvular leaks around prosthetic mitral valves. A transcatheter stented valve, which is used as a **transcatheter aortic valve replacement (TAVR)** device, can be used to open a degenerated mitral bioprosthetic valve in any position (aortic, mitral, tricuspid, or pulmonary). Transcatheter



▲ **Figure 10–3.** Algorithm for intervention in secondary mitral regurgitation. AF, atrial fibrillation; CABG, coronary artery bypass graft; ERO, effective regurgitant orifice; GDMT, guideline-directed management and therapy; HF, heart failure; LVESD, LV end-systolic dimension; MR, mitral regurgitation; MV, mitral valve; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume. (Reprinted from Journal of the American College of Cardiology,77, Otto CM et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, e25–e197, 2021, with permission from Elsevier.)

valve replacement has also been attempted in small series to repair mitral regurgitation following mitral valve repair with mixed results. Finally, the first cases of a stented mitral valve prosthesis to replace the entire mitral valve have been reported. Abbott has initiated the SUMMIT trial, a US-based pivotal trial utilizing the Tendyne percutaneous mitral valve replacement device. The mitral valve and aortic valve share a common "annulus" and some of the early attempts at percutaneous valve replacement have failed due to obstruction of the aortic outflow.

When to Refer

- All patients with more than mild mitral regurgitation should be referred to a cardiologist for an evaluation.
- Serial examinations and echocardiograms should be obtained and surgical referral made if there is an increase in the LV end-systolic dimensions, a fall in the LVEF to less than 60%, symptoms, evidence for pulmonary hypertension, or the new onset of atrial fibrillation.
- There is evidence that mitral valve repair should be done early in the course of the disease to improve mortality and morbidity.
- Treatment in severe mitral regurgitation in a patient with a dilated cardiomyopathy may be of benefit.

Ailawadi G et al; EVEREST II Investigators. One-year outcomes after MitraClip for functional mitral regurgitation. Circulation. 2019;139:37. [PMID: 30586701]

Grayburn PA et al. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. JACC Cardiovasc Imaging. 2019;12:353. [PMID: 30553663]

Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2021; 77:450. [PMID: 33342587]

Pibarot P et al. MITRA-FR versus COAPT: lessons from two trials with diametrically opposed results. Eur Heart J Cardiovasc Imaging. 2019;20:620. [PMID: 31115470]

AORTIC STENOSIS

ESSENTIALS OF DIAGNOSIS

- Congenital bicuspid aortic valve (usually asymptomatic until middle or old age).
- "Degenerative" or calcific aortic stenosis; similar risk factors as atherosclerosis (symptoms usually in the elderly).
- Visual observation of immobile aortic valve plus a valve area of less than 1.0 cm^2 define severe disease; low-gradient but severe aortic stenosis can thus be recognized when the stroke volume is reduced.
- Echocardiography/Doppler is diagnostic.
- Surgery typically indicated for symptoms. TAVR is approved for patients with calcific aortic stenosis.
- Intervention appropriate even in asymptomatic patients with super-severe aortic stenosis (mean gradient greater than 55 mm Hg) or when undergoing heart surgery for other reasons (eg, coronary artery bypass grafting [CABG]).
- BNP is a marker of early LV myocardial failure, and high levels (three times normal) suggest poor prognosis and can be an indication for intervention.

General Considerations

There are two common clinical scenarios in which aortic stenosis is prevalent. The first is due to a congenitally abnormal **unicuspid** or **bicuspid valve,** rather than tricuspid. Symptoms can occur in young or adolescent individuals if the stenosis is severe, but more often emerge at age 50–65 years when calcification and degeneration of the valve become manifest. A dilated ascending aorta, due to an intrinsic defect in the aortic root media and the hemodynamic effects of the eccentric aortic jet, may accompany the bicuspid valve in about half of these patients. Coarctation of the aorta is also seen in a number of patients with congenital aortic stenosis. Offspring of patients with a bicuspid valve have a much higher incidence of the disease in either the valve, the aorta, or both (up to 30% in some series).

A second, more common pathologic process, **degenerative** or **calcific aortic stenosis**, is thought to be related to calcium deposition due to processes similar to those that occur in atherosclerotic vascular disease. Approximately 25% of patients over age 65 years and 35% of those over age 70 years have echocardiographic evidence of aortic valve thickening (sclerosis). About 10–20% of these will progress to hemodynamically significant aortic stenosis over a period of 10–15 years. Certain genetic markers are associated with aortic stenosis (most notably Notch 1), so a genetic component appears a likely contributor, at least in some patients. Other associated genetic markers have also been described.

Aortic stenosis has become the most common surgical valve lesion in developed countries, and many patients are elderly. The risk factors include hypertension, hypercholesterolemia, and smoking. HCM may also coexist with valvular aortic stenosis.

Clinical Findings

A. Symptoms and Signs

Slightly narrowed, thickened, or roughened valves **(aortic sclerosis)** or aortic dilation may contribute to the typical ejection murmur of aortic stenosis. In mild or moderate cases where the valve is still pliable, an ejection click may precede the murmur and the closure of the valve (S_2) is preserved. The characteristic systolic ejection murmur is heard at the aortic area and is usually transmitted to the neck and apex. In severe aortic stenosis, a palpable LV heave or thrill, a weak to absent aortic second sound, or reversed splitting of the second sound is present (see Table 10–1). In some cases, only the high-pitched components of the murmur are heard at the apex, and the murmur may sound like mitral regurgitation (the so-called **Gallavardin phenomenon**). When the valve area is less than 0.8–1.0 cm^2 (normal, 3–4 cm^2), ventricular systole becomes prolonged and the typical carotid pulse pattern of delayed upstroke and low amplitude is present. A delayed upstroke, though, is an unreliable finding in older patients with extensive arteriosclerotic vascular disease and a stiff, noncompliant aorta. LVH increases progressively due to the pressure overload, eventually resulting in elevation of ventricular end-diastolic pressure. Cardiac output is maintained until the stenosis is severe. LV failure, angina pectoris, or syncope may be presenting symptoms of significant aortic stenosis; importantly, all symptoms tend to first occur with exertion.

B. Redefining Severe Aortic Stenosis

There are four different anatomic syndromes that occur in patients with severe aortic stenosis. The common underlying measure of **severe aortic stenosis** is an aortic valve area of less than 1.0 cm^2 and echocardiographic evidence of an immobile aortic valve. In patients with a normal LVEF and normal cardiac output, the threshold for intervention is a peak aortic gradient of greater than 64 mm Hg and mean aortic gradient of greater than 40 mm Hg. In the same situation, **super-severe aortic stenosis** is defined as a mean gradient of greater than 55 mm Hg or peak aortic velocity greater than 5 m/seconds by Doppler.

In some patients with an aortic valve area of less than 1.0 cm^2 with a low cardiac output and stroke volume, the mean gradient may be less than 40 mm Hg. This can occur when the LV systolic function is poor **(low-gradient severe aortic stenosis with low LVEF)** or when the LV systolic function is normal **(paradoxical low-flow severe aortic stenosis with a normal LVEF).** Low flow (low output) in

these situations is defined by an echocardiographic stroke volume index of less than 35 mL/minute/m^2. Prognosis in patients with low gradient, low valve area, low output, and a normal LVEF aortic stenosis may actually be worse than in patients with the traditional high gradient, low valve area, normal output, and normal LVEF aortic stenosis. If low-flow severe aortic stenosis is present in the face of a low LVEF, provocative testing with dobutamine or nitroprusside is sometimes warranted to increase the stroke volume to discover if a mean aortic valve gradient of at least 40 mm Hg can be demonstrated without increasing the aortic valve area. If the aortic valve area can be made to increase and a mean gradient of greater than 40 mm Hg cannot be demonstrated by inotropic challenge, the presumption is that the low gradient is due to an associated cardiomyopathy and not the aortic valve stenosis. In this latter situation intervention is not indicated. The guidelines acknowledge these four situations (Table 10–3). Intervention is indicated in super-severe aortic stenosis even without demonstrable symptoms (grade C) and in any of the other situations when symptoms are present: D1 defines the symptomatic high-gradient patient; D2 the symptomatic low-flow, low-gradient patient with low LVEF; and D3 the symptomatic low-flow, low-gradient patient with normal LVEF.

Symptoms of LV failure may be sudden in onset or may progress gradually. Angina pectoris frequently occurs in aortic stenosis due to underperfusion of the endocardium. Of patients with calcific aortic stenosis and angina, half have significant associated CAD. Syncope, a late finding, occurs with exertion as the LV pressure rises, stimulating the LV baroreceptors to cause peripheral vasodilation. This vasodilation results in the need for an increase in stroke volume, which increases the LV systolic pressure again, creating a cycle of vasodilation and stimulation of the baroreceptors that eventually results in a drop in systemic BP, as the stenotic valve prevents further increase in stroke volume. Less commonly, syncope may be due to arrhythmias (usually ventricular tachycardia but sometimes AV block as calcific invasion of the conduction system from the aortic valve may occur).

Table 10–3. Summary of AHA/ACC guideline definitions of symptomatic severe aortic stenosis.

Category of Severe Aortic Stenosis[1]	Properties
High Gradient	
High gradient	> 4.0 m/seconds Doppler jet velocity > 40 mm Hg mean gradient
Super-severe	> 5.0 m/seconds Doppler jet velocity > 55 mm Hg mean gradient
Low Gradient	
Low flow	Reduced LVEF (< 50%)
Low flow	Paradoxical with normal LVEF (> 50%)

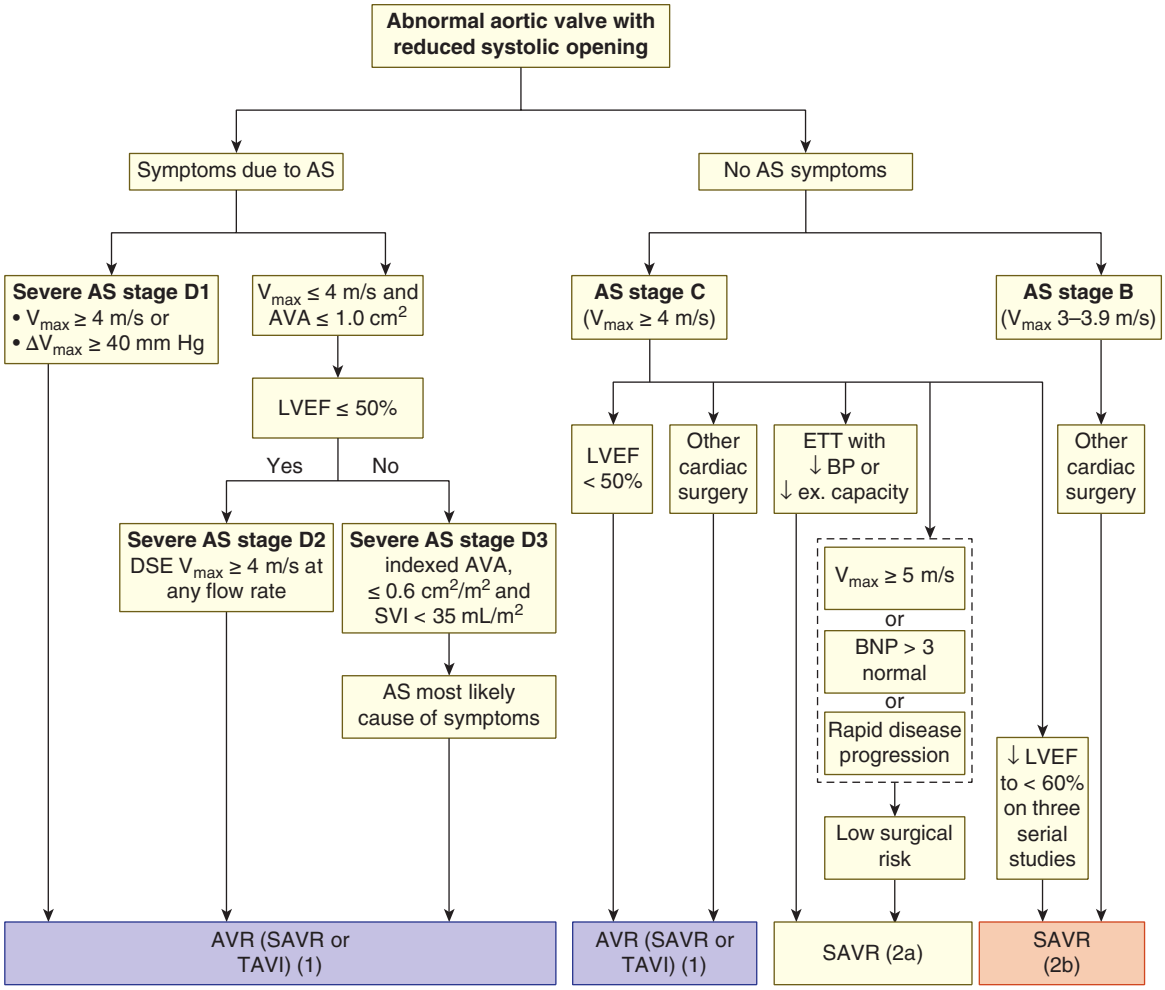
[1]All categories of severe aortic stenosis have abnormal systolic opening of the aortic valve and an aortic valve area < 1.0 cm^2.

C. Diagnostic Studies

The ECG reveals LVH or secondary repolarization changes in most patients but can be normal in up to 10%. The chest radiograph may show (1) a normal or enlarged cardiac silhouette, (2) calcification of the aortic valve, and (3) dilation or calcification (or both) of the ascending aorta. The echocardiogram provides useful data about aortic valve calcification and leaflet opening, the severity of LV wall thickness, and overall ventricular function, while Doppler can provide an excellent estimate of the aortic valve gradient. Valve area estimation by echocardiography is a critical component of the diagnosis of aortic stenosis due to issues such as paradoxical low-flow aortic stenosis (low-gradient, low-flow, normal LVEF patients). Likewise, the echocardiography/Doppler can estimate the stroke volume index used to define the low-flow state when the valve area is small but the gradient is less than 40 mm Hg. Cardiac catheterization mostly provides an assessment of the hemodynamic consequence of the aortic stenosis, and the anatomy of the coronary arteries. Catheterization data can be important when there is a discrepancy between symptoms and the echocardiography/Doppler information of aortic stenosis severity. In younger patients and in patients with high aortic gradients, the aortic valve need not be crossed at catheterization. Aortic regurgitation can be semiquantified by aortic root angiography. Either BNP or NT-proBNP may provide additional prognostic data in the setting of poor LV function and aortic stenosis. A BNP greater than 550 pg/mL has been associated with a poor outcome in these patients regardless of the results of dobutamine testing. Current guidelines suggest intervention when the NT-proBNP is three times normal (class IIa indication). Stress testing can be done cautiously in patients in whom the aortic stenosis severity does not match the reported symptoms in order to confirm the reported clinical status. It should *not* be done in patients with super-severe aortic stenosis.

Prognosis & Treatment

Valve intervention is warranted in all patients who have symptomatic severe aortic stenosis (Figure 10–4). There are also times when asymptomatic aortic stenosis should undergo intervention. Asymptomatic patients with severe aortic stenosis (aortic valve area less than 1.0 cm^2) should generally undergo intervention according to the following guidelines: (1) they are undergoing other cardiac surgery (ie, CABG), (2) there is evidence for a reduced LVEF (less than 50%), (3) when the mean gradient exceeds 55 mm Hg (peak velocity greater than 5 m/seconds), (4) when there is exercise intolerance or when the BP falls more than 10 mm Hg with exercise, (5) when there is severe valvular calcium, (6) when there is evidence of a rapid increase in the peak aortic gradient (more than 0.3 m/seconds/year), (7) when there has been a progressive decrease in the LVEF, or (8) when the NT-proBNP is three times normal. Following the onset of heart failure, angina, or syncope, the prognosis without surgery is poor (50% 3-year mortality rate). Medical treatment may stabilize patients in heart failure, but intervention is indicated for all symptomatic patients with evidence of significant aortic stenosis.



▲ **Figure 10–4.** Algorithm for the timing of intervention in aortic valve stenosis. AS, aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area index; AVR, aortic valve replacement; BP, blood pressure; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; ΔP_{mean}, mean systolic pressure gradient between LV and aorta; SAVR, surgical aortic valve replacement; SVI, stroke volume index; TAVI, transcatheter aortic valve implantation; TAVR, transcatheter aortic valve replacement; V_{max}, maximum velocity. (Reprinted from Journal of the American College of Cardiology,77, Otto CM et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, e25–e197, 2021, with permission from Elsevier.)

The surgical mortality rate for valve replacement is low, even in older adults, and ranges from 2% to 5%. This low risk is due to the dramatic hemodynamic improvement that occurs with relief of the increased afterload. Mortality rates are substantially higher when there is an associated ischemic cardiomyopathy. Severe coronary lesions are usually bypassed at the same time as aortic valve replacement (AVR), although there are few data to suggest this practice affects outcome. In some cases, a staged procedure with stenting of the coronaries prior to surgery may be considered, especially if a percutaneous AVR approach is being considered. Around one-third to one-half of all patients with aortic stenosis have significant CAD, so this is a common concern. With the success of **transcatheter aortic valve replacement (TAVR)** or **transcatheter aortic valve implantation (TAVI),** the treatment options have greatly expanded for many patients with severe aortic stenosis. For this reason, a **Heart Valve Team** approach bringing together invasive and noninvasive cardiologists, radiologists, anesthesiologists, and cardiac surgeons is mandatory; clinical factors (such as frailty) and anatomic features (such as a calcified aorta, vascular access, etc) can affect the decision making.

Medical therapy to reduce the progression of disease has *not* been effective to date. Statins have been assessed in four major clinical trials. None revealed any benefit on the

progression of aortic stenosis or on clinical outcomes despite the association of aortic stenosis with atherosclerosis. If patients with aortic stenosis have concomitant CAD, the guidelines for the use of statins should be followed. Efforts to reduce stenosis progression by blockage of the renin-angiotensin system have also been ineffective, though they are currently recommended for patients who have undergone TAVR. Control of systemic hypertension is an important adjunct, and inadequate systemic BP control is all too common due to unreasonable concerns about providing too much afterload reduction in patients with aortic stenosis. Normal systemic BP is important to maintain as the LV is affected by the total afterload (systemic BP plus the aortic valve gradient).

The interventional options in patients with aortic valve stenosis has expanded with the use of TAVR and depend on the patient's lifestyle and age. The algorithm to decide when an AVR is appropriate in various situations is outlined in Figure 10–5.

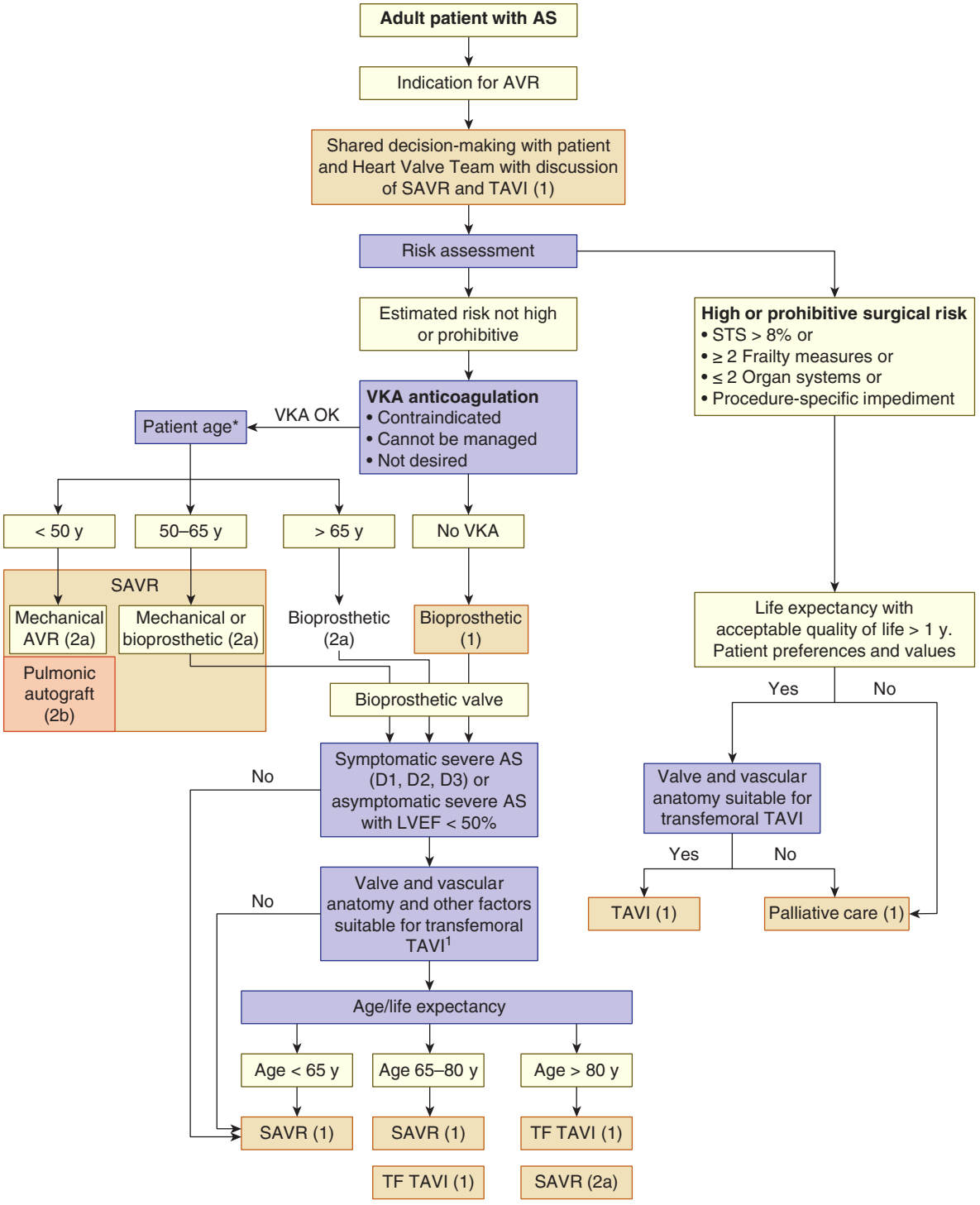
TAVR has been shown to be equivalent to surgical AVR (SAVR) in all the randomized trials of symptomatic patients, including those at low risk for surgery (less than 4%). Surgery is recommended for patients younger than 65 years or with a life expectancy of more than 20 years. TAVR is recommended for all patients older than 80 years. Either SAVR or TAVR can be considered for all patients between 65 and 80 years. The decision about whether to perform SAVR or TAVR should be made by the Heart Team; anatomic issues (such as an enlarged aorta, a coronary that might be trapped by a leaflet when the valve is inserted, an annulus too large or too small, extensive LV outflow tract calcium, etc) are often the deciding factors for whether TAVR can be done.

In young and adolescent patients, percutaneous balloon valvuloplasty still has a very small role. Balloon valvuloplasty is associated with early restenosis in the elderly population and, thus, is rarely used except as a temporizing measure prior to a more permanent SAVR or TAVR. Data suggest aortic balloon valvuloplasty in elderly people has an advantage only in those with preserved LV function, and such patients are usually excellent candidates for SAVR or TAVR.

The **Ross procedure** is generally still considered a viable option in younger patients with a bicuspid valve, and it is performed by moving the patient's own pulmonary valve and a portion of its root to the aortic position and replacing the pulmonary valve with a homograft (or rarely a bioprosthetic valve). The coronaries require reimplantation. However, dilation of the pulmonary valve autograft and consequent aortic regurgitation, plus early stenosis of the pulmonary homograft in the pulmonary position, has reduced the enthusiasm for this approach in most institutions. Current guidelines suggest the Ross procedure should only be considered in those younger than 50 years. Middle-aged and younger adults generally can tolerate the anticoagulation therapy necessary for the use of mechanical aortic valves, so patients younger than 50 years generally undergo AVR with a bileaflet mechanical valve. If the aortic root is severely dilated as well (greater than 4.5 cm), then the valve may be housed in a Dacron sheath (**Bentall procedure**) and the root replaced along with the aortic valve. Alternatively, a human homograft root and valve replacement can be used. In patients older than 50 years, bioprosthetic (either porcine or bovine pericardial) valves with a life expectancy of about 10–15 years are routinely used instead of mechanical valves to avoid need for anticoagulation. Data favor the bovine pericardial valve over the porcine aortic valve. Bioprosthetic valve degeneration in the larger valves can be potentially repaired by percutaneous valve-in-valve TAVR. If the aortic annulus is small, a bioprosthetic valve with a short sheath can be sewn to the aortic wall (the stentless AVR) rather than sewing the prosthetic annulus to the aortic annulus. (Annulus is a relative term when speaking of the aortic valve, since there is no true annulus.) Another popular surgical option when the aorta is enlarged is the use of the **Wheat procedure;** it involves aortic root replacement above the coronary arteries and replacement of the aortic valve below the coronary arteries. The coronary arteries thus remain attached to the native aorta between the new graft and prosthetic valve rather than being reimplanted onto an artificial sheath or homograft. Newer aortic valve replacements can be placed quickly through a small incision and often require only three stitches to anchor (ie, the Perceval or Intuity valve replacements). These can shorten pump times at surgery.

In patients with a bicuspid aortic valve, there is an associated ascending aortic aneurysm in about half. If the maximal dimension of the aortic root is greater than 5.5 cm, it is recommended to proceed with root replacement regardless of the severity of the aortic valve disease. It is also appropriate to intervene when the maximal aortic root size is greater than 5.0 cm in diameter if there is a family history of aortic dissection or the aortic root size increases by more than 0.5 cm in 1 year. The aortic valve may be replaced at the same time if at least moderate aortic stenosis is present or may be either left alone or repaired (valve sparing operation). If there is an indication for AVR and the root is greater than 4.5 cm in diameter, root replacement is also recommended at the time of SAVR.

The use of mechanical versus bioprosthetic AVR has changed over time. A bioprosthetic valve is acceptable for patients at any age for whom anticoagulant therapy is contraindicated, not desired, or cannot be managed, and is preferred in patients over the age of 65. An aortic mechanical valve should be used in patients younger than 50 years of age who can take warfarin. **Anticoagulation** with warfarin is required with the use of mechanical aortic valves, and the international normalized ratio (INR) should be maintained between 2.0 and 3.0 for bileaflet valves. In general, mechanical aortic valves are less subject to thrombosis than mechanical mitral valves and do not require bridging with enoxaparin unless there are other thromboembolic risk factors or it is an older generation AVR. Low-dose aspirin (eg, 81 mg daily) is recommended if there is a low bleeding risk. Some newer bileaflet mechanical valves (On-X) allow for a lower INR range from 1.5 to 2.0. Clopidogrel is recommended for the first 6 months after TAVR in combination with lifelong low-dose aspirin therapy (dual antiplatelet therapy). DOACs are *not* recommended for any mechanical valves but may be used in patients with



▲ **Figure 10–5.** Algorithm for the type of valvular intervention in aortic valve stenosis. AS, aortic stenosis; AVR, aortic valve replacement; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; TF, transfemoral; VKA, vitamin K antagonist. (Reprinted from Journal of the American College of Cardiology,77, Otto CM et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, e25–e197, 2021, with permission from Elsevier.)

a bioprosthetic AVR if treating atrial fibrillation or venous thrombosis.

The use of TAVR has grown dramatically. The Edwards SAPIEN valve is a balloon-expandable valvular stent, while the CoreValve is a valvular stent that self-expands when pushed out of the catheter sheath. Cost remains a major issue. The cost of TAVR is similar to SAVR, mostly due to the cost of the valve itself. All of the professional societies stress the importance of a Heart Valve Team when considering aortic stenosis intervention.

TAVR is also being used more frequently in "valve-in-valve" procedures to reduce the gradient in patients with prosthetic valve dysfunction (regardless of whether in the aortic, mitral, tricuspid, or pulmonary position). While the results of TAVR in patients with bicuspid aortic valves (as opposed to tricuspid) have been less impressive, newer modifications have improved the success rates in these anatomic situations as well. This is supported by data from the TVT registry showing similar procedural and 1-year outcomes for patients with bicuspid or tricuspid aortic valve stenosis.

When to Refer

- All patients with echocardiographic evidence for mild-to-moderate aortic stenosis (estimated peak valve gradient greater than 30 mm Hg by echocardiography/Doppler) should be referred to a cardiologist for evaluation and to determine the frequency of follow-up.
- Any patients with symptoms suggestive of aortic stenosis (ie, exertional symptoms of chest pressure, shortness of breath, or presyncope) should be seen by a cardiologist.

Halim SA et al. Outcomes of transcatheter aortic valve replacement in patients with bicuspid aortic valve disease: a report from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Circulation. 2020;141:1071. [PMID: 32098500]

Mack MJ et al; PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380:1695. [PMID: 30883058]

Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2021; 77:450. [PMID: 33342587]

Popma JJ et al; Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med. 2019;380:1706. [PMID: 30883053]

AORTIC REGURGITATION

ESSENTIALS OF DIAGNOSIS

- Usually asymptomatic until middle age; presents with left-sided failure or rarely chest pain.
- Echocardiography/Doppler is diagnostic.
- Surgery for symptoms, EF < 50%, LV end-systolic dimension > 50 mm, or LV end-diastolic dimension > 65 mm.

General Considerations

Of all patients with isolated aortic valve disease, about 13% have predominately aortic regurgitation. Rheumatic aortic regurgitation has become much less common than in the preantibiotic era, and nonrheumatic causes now predominate. These include congenitally bicuspid valves, infective endocarditis, and hypertension. Many patients also have aortic regurgitation secondary to aortic root diseases, such as that associated with Marfan syndrome or aortic dissection. Rarely, inflammatory diseases, such as ankylosing spondylitis, may be implicated.

Clinical Findings

A. Symptoms and Signs

The clinical presentation is determined by the rapidity with which regurgitation develops. In **chronic aortic regurgitation,** the only sign for many years may be a soft aortic diastolic murmur. As the severity of the aortic regurgitation increases, diastolic BP falls, and the LV progressively enlarges. Most patients remain asymptomatic for long periods even at this point. LV failure is a late event and may be sudden in onset. Exertional dyspnea and fatigue are the most frequent symptoms, but paroxysmal nocturnal dyspnea and pulmonary edema may also occur. Angina pectoris or atypical chest pain may occasionally be present. Associated CAD and presyncope or syncope are less common than in aortic stenosis.

Hemodynamically, because of compensatory LV dilation, patients eject a large stroke volume, which is adequate to maintain forward cardiac output until late in the course of the disease. LV diastolic pressure may rise when heart failure occurs. Abnormal LV systolic function as manifested by reduced EF (less than 50%) and increasing end-systolic LV volume (greater than 5.0 cm) are signs that surgical intervention is warranted.

The major physical findings in chronic aortic regurgitation relate to the high stroke volume being ejected into the systemic vascular system with rapid runoff as the regurgitation takes place (see Table 10–1). This results in a **wide arterial pulse pressure.** The pulse has a rapid rise and fall (**water-hammer pulse** or **Corrigan pulse**), with an elevated systolic and low diastolic pressure. The large stroke volume and flow back into the heart are also responsible for characteristic findings, such as **Quincke pulses** (nailbed capillary pulsations), **Duroziez sign** (to-and-fro murmur over a partially compressed femoral peripheral artery), and **Musset sign** (head bob with each pulse). In younger patients, the increased stroke volume may summate with the pressure wave reflected from the periphery and create a higher than expected systolic pressure in the lower extremities compared with the central aorta. Since the peripheral bed is much larger in the leg than the arm, the BP in the leg may be over 40 mm Hg higher than in the arm (**Hill sign**) in severe aortic regurgitation. The apical impulse is prominent, laterally displaced, usually hyperdynamic, and may be sustained. A systolic flow murmur is usually present and may be quite soft and localized; the aortic diastolic murmur is usually high-pitched

and decrescendo. A mid or late diastolic low-pitched mitral murmur (**Austin Flint murmur**) may be heard in advanced aortic regurgitation, owing to relative obstruction of mitral inflow produced by partial closure of the mitral valve by the rapidly rising LV diastolic pressure due to the aortic regurgitation.

In **acute aortic regurgitation** (usually from aortic dissection or infective endocarditis), LV failure is manifested primarily as pulmonary edema and may develop rapidly; surgery is urgently required in such cases. Patients with acute aortic regurgitation do not have the dilated LV of chronic aortic regurgitation and the extra LV volume is handled poorly. For the same reason, the diastolic murmur is shorter, may be minimal in intensity, and the pulse pressure may not be widened—making clinical diagnosis difficult. The mitral valve may close prematurely even before LV systole has been initiated (**preclosure**) due to the rapid rise in the LV diastolic pressure, and the first heart sound is thus diminished or inaudible. Preclosure of the mitral valve can be readily detected on echocardiography and is considered an indication for urgent surgical intervention.

B. Diagnostic Studies

The ECG usually shows moderate to severe LVH. Radiographs show cardiomegaly with LV prominence and sometimes a dilated aorta.

Echocardiography demonstrates the major diagnostic features, including whether the lesion includes the proximal aortic root and what valvular pathology is present. **Annual assessments of LV size and function are critical in determining the timing for valve replacement when the aortic regurgitation is severe.** The 2020 ACC/AHA valvular guideline provides criteria for assessing the severity of aortic regurgitation. Cardiac MRI and CT can estimate aortic root size, particularly when there is concern for an ascending aneurysm. MRI can provide a regurgitant fraction to help confirm severity. Cardiac catheterization may be unnecessary in younger patients, particularly those with acute aortic regurgitation, but can help define hemodynamics, aortic root abnormalities, and associated CAD preoperatively in older patients. Increasing data are emerging that serum BNP or NT-proBNP may be an early sign of LV dysfunction, and it is possible that these data will be added to recommendations for surgical intervention in the future.

Treatment & Prognosis

Aortic regurgitation that appears or worsens during or after an episode of infective endocarditis or aortic dissection may lead to acute severe LV failure or subacute progression over weeks or months. The former usually presents as pulmonary edema; surgical replacement of the valve is indicated even during active infection. These patients may be transiently improved or stabilized by vasodilators.

Chronic aortic regurgitation may be tolerated for many years, but the prognosis without surgery becomes poor when symptoms occur. Since aortic regurgitation places both a preload (volume) and afterload increase on the LV, medications that decrease afterload can reduce regurgitation severity, although there are no convincing data that afterload reduction alters mortality. **Recommendations advocate afterload reduction in aortic regurgitation only when there is associated systolic hypertension (systolic BP greater than 140 mm Hg).** Afterload reduction in normotensive patients does not appear warranted. ARBs, rather than beta-blockers, are the preferred additions to the medical therapy in patients with an enlarged aorta, such as in Marfan syndrome, because of the theoretical ability of an ARB to reduce aortic stiffness (by blocking TGF-beta) and to slow the rate of aortic dilation. However, clinical trials evaluating the efficacy of ARBs to reduce aortic stiffness and slow the rate of aortic dilation have not yielded a positive outcome to support their use.

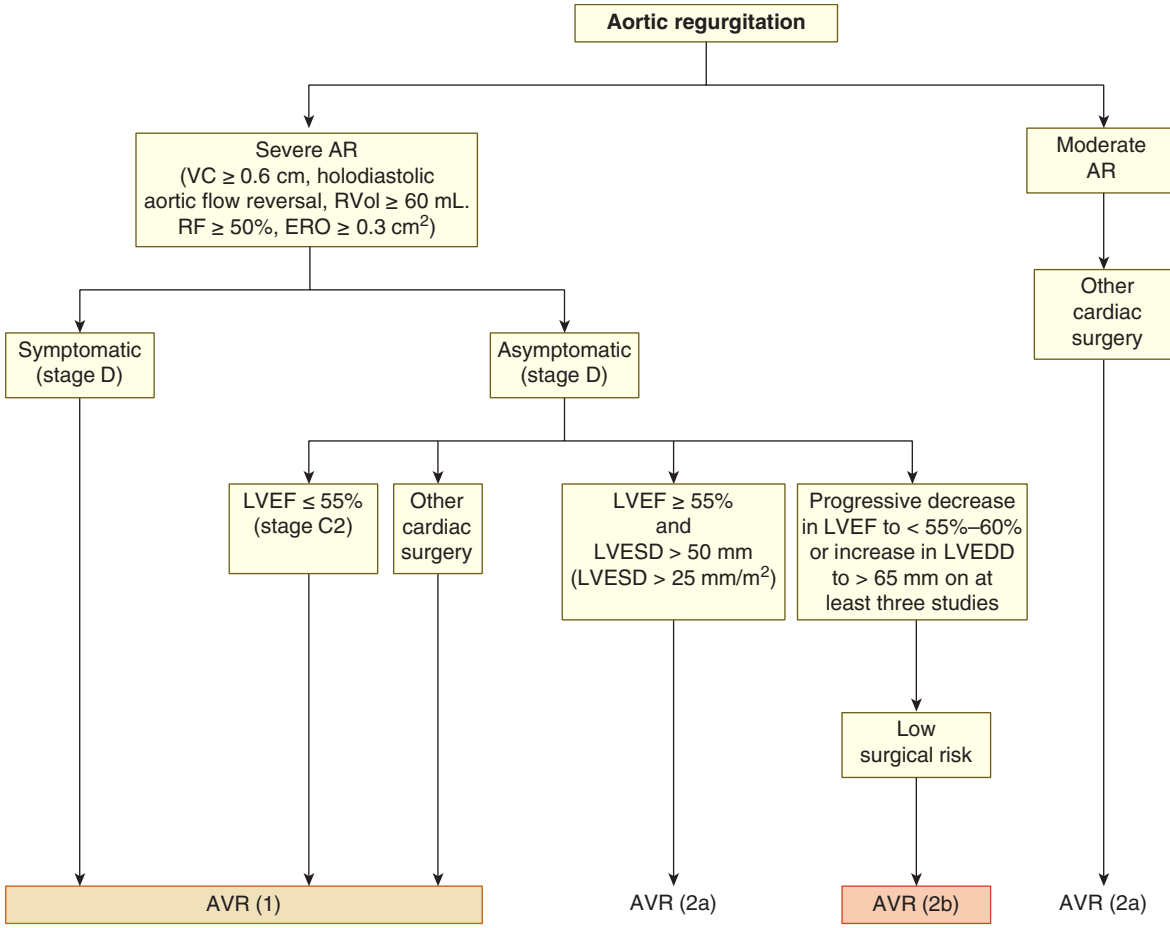
Surgery is indicated once symptoms emerge or for any evidence of LV dysfunction (as exhibited by a reduction in the LVEF to less than 55% or increase in the LV end-systolic diameter to greater than 50 mm by echocardiography). In addition, it is suggested that surgery should be considered even when the LV becomes excessively enlarged (LV end-diastolic diameter greater than 65 mm). Guidelines also suggest it be considered (class IIb) if serial imaging reveals a progressive increase in the size of the LV (Figure 10–6).

The issues with AVR covered in the above section concerning aortic stenosis pertain here. Early trials of TAVR had a high incidence of postprocedural residual aortic regurgitation (18.8% in one trial). Newer TAVR valves have greatly reduced residual aortic regurgitation when used in patients with pure native aortic regurgitation (4.2%). In multivariable analysis, postprocedural at least moderate aortic regurgitation was independently associated with 1-year all-cause mortality. Compared with the early-generation devices, TAVR using the new-generation devices was associated with improved procedural outcomes in treating patients with pure native aortic regurgitation. In patients with pure native aortic regurgitation, significant postprocedural aortic regurgitation was independently associated with increased mortality.

Aortic regurgitation due to a paravalvular prosthetic valve defect can occasionally be occluded with percutaneous occluder devices. The choice of prosthetic valve for AVR depends on the patient's age and compatibility with warfarin anticoagulation similar to the choices for AVR in aortic stenosis.

The operative mortality for AVR is usually in the 3–5% range. Aortic regurgitation due to aortic root disease requires repair or replacement of the root as well as surgical treatment of the aortic valve. Though valve-sparing operations have improved recently, most patients with root replacement undergo valve replacement at the same time. Root replacement in association with valve replacement may require anastomosis of the coronary arteries, and thus the procedure is more complex than valve replacement alone. The Wheat procedure replaces the aortic root but spares the area where the coronaries attach to avoid the necessity for their reimplantation. Following any aortic valve surgery, LV size usually decreases and LV function generally improves even when the baseline EF is depressed.

Repair of the aortic root in patients with a bicuspid valve should be done once the root diameter exceeds 5.5 cm



▲ **Figure 10–6.** Algorithm for intervention in aortic regurgitation. AR, aortic regurgitation; AVR, aortic valve replacement; EDD, end-diastolic dimension; ERO, effective regurgitant orifice; LVESD, LV end-systolic dimension; RF, regurgitant fraction; RVol, regurgitant volume; VC, vena contracta. (Reprinted from Journal of the American College of Cardiology,77, Otto CM et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, e25-e197, 2021, with permission from Elsevier.)

regardless of aortic valve disease severity. There are data that dissection is much more prevalent when the aortic root diameter exceeds 6.0 cm, and the general sense is not to let it approach that size. Patients with risk factors (family history of dissection or an increase in the diameter of the root greater than 0.5 cm in 1 year) should have the aorta repaired when the maximal dimension exceeds 5.0 cm. The following classifications summarize when to operate on the aortic root in patients with a bicuspid aortic valve based on the guidelines:

Class I indication (LOE C): aortic root diameter at sinuses or ascending aorta greater than 5.5 cm (regardless of need for AVR).

Class IIa indication (LOE C): aortic root diameter at sinuses or ascending aorta greater than 5.0 cm when there are associated risk factors (family history of dissection or increase in size more than 0.5 cm in 1 year).

Class IIa indication (LOE C): aortic root diameter greater than 4.5 cm if patient undergoing AVR for valvular reasons.

When to Refer

- Patients with audible aortic regurgitation should be seen, at least initially, by a cardiologist who can determine whether the patient needs follow-up.
- Patients with a dilated aortic root should be monitored by a cardiologist, since imaging studies other than the chest radiograph or echocardiogram may be required to decide surgical timing.

O'Gara PT et al. Timing of valve interventions in patients with chronic aortic regurgitation: are we waiting too long? J Am Coll Cardiol. 2019;73:1753. [PMID: 30846337]

Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2021;77:450. [PMID: 33342587]

TRICUSPID STENOSIS

ESSENTIALS OF DIAGNOSIS

- Female predominance.
- History of rheumatic heart disease most likely. Carcinoid disease and prosthetic valve degeneration are the most common etiologies in the United States.
- Echocardiography/Doppler is diagnostic.

General Considerations

Tricuspid stenosis is rare, affecting less than 1% of the population in developed countries and less than 3% worldwide. Native valve tricuspid valve stenosis is usually rheumatic in origin. In the United States, tricuspid stenosis is more commonly due to prior tricuspid valve repair or replacement or to the carcinoid syndrome. The incidence of tricuspid stenosis after tricuspid valve replacement increases considerably after 8 years post surgery. Tricuspid regurgitation frequently accompanies the lesion. It should be suspected when right heart failure appears in the course of mitral valve disease or in the postoperative period after tricuspid valve repair or replacement.

Clinical Findings

A. Symptoms and Signs

Tricuspid stenosis is characterized by right heart failure with hepatomegaly, ascites, and dependent edema. In sinus rhythm, a giant *a* wave is seen in the JVP, which is also elevated (see Table 10–1). The typical **diastolic rumble** along the lower left sternal border mimics mitral stenosis, though in tricuspid stenosis the rumble *increases with inspiration*. In sinus rhythm, a presystolic liver pulsation may be found. It should be considered when patients exhibit signs of carcinoid syndrome.

B. Diagnostic Studies

In the absence of atrial fibrillation, the ECG reveals RA enlargement. The chest radiograph may show marked cardiomegaly with a normal PA size. A dilated superior vena cava and azygous vein may be evident.

The normal valve area of the tricuspid valve is 10 cm^2, so significant stenosis must be present to produce a gradient. Hemodynamically, a mean diastolic pressure gradient greater than 5 mm Hg is considered significant, although even a 2 mm Hg gradient can be considered abnormal. This can be demonstrated by echocardiography or cardiac catheterization. The 2017 update of the 2014 AHA/ACC guidelines suggests a tricuspid valve area of less than 1.0 cm^2 and a pressure half-time longer than 190 msec should be defined as significant because the gradient may vary depending on the heart rate.

Treatment & Prognosis

Tricuspid stenosis may be progressive, eventually causing severe right-sided heart failure. Initial therapy is directed at reducing the fluid congestion, with diuretics the mainstay (see Treatment, Heart Failure). When there is considerable bowel edema, torsemide or bumetanide may have an advantage over other loop diuretics, such as furosemide, because they are better absorbed from the gut. Aldosterone inhibitors also help, particularly if there is liver engorgement or ascites. Neither surgical nor percutaneous valvuloplasty is particularly effective for relief of tricuspid stenosis, as residual tricuspid regurgitation is common. Tricuspid valve replacement is the preferred surgical approach. Mechanical tricuspid valve replacement is rarely done because the low flow predisposes to thrombosis and because the mechanical valve cannot be crossed should the need arise for right heart catheterization or pacemaker implantation. Therefore, bioprosthetic valves are almost always preferred. Often tricuspid valve replacement is performed in conjunction with mitral valve replacement for rheumatic mitral stenosis or regurgitation. Percutaneous transcatheter valve replacement (stented valve) has been used in degenerative tricuspid prosthetic valve stenosis and a percutaneous tricuspid valve replacement device is being investigated. The indications for valve replacement in severe tricuspid stenosis are straightforward:

Class I indication (LOE C): at time of operation for left-sided valve disease.

Class I indication (LOE C): if symptomatic.

Class IIb indication (LOE C): rarely percutaneous balloon commissurotomy for isolated tricuspid stenosis in high-risk patients with no significant tricuspid regurgitation.

When to Refer

All patients with any evidence for tricuspid stenosis on an echocardiogram should be seen and monitored by a cardiologist to assess when intervention may be required.

Hirata K et al. Bioprosthetic tricuspid valve stenosis: a case series. Eur Heart J Case Rep. 2019;3:ytz110. [PMID: 31367735]

TRICUSPID REGURGITATION

ESSENTIALS OF DIAGNOSIS

- Frequently occurs in patients with pulmonary or cardiac disease with pressure or volume overload on the right ventricle.
- Tricuspid valve regurgitation from pacemaker lead placement is becoming more common.
- Echocardiography useful in determining cause (low- or high-pressure tricuspid regurgitation).

General Considerations

Tricuspid valvular regurgitation often occurs whenever there is RV dilation from any cause. As tricuspid regurgitation increases, the RV size increases further pulling the valve open due to chordal and papillary muscle displacement. This, in turn, worsens the severity of the tricuspid regurgitation. In addition, the tricuspid annulus is shaped like a horse's saddle. With RV failure, the annulus flattens and becomes elliptical, further distorting the relationship between the leaflets and chordal attachments. In most cases, the cause of the tricuspid regurgitation is the RV geometry (functional) and not primary tricuspid valve disease. An enlarged, dilated RV may be present if there is RV systolic hypertension from valvular or subvalvular pulmonary valve stenosis, pulmonary hypertension for any reason, in severe pulmonary valve regurgitation, or in cardiomyopathy. The RV may also be injured from an MI or may be inherently dilated due to infiltrative diseases (RV dysplasia or sarcoidosis). RV dilation often occurs secondary to left heart failure. Inherent abnormalities of the tricuspid valve include **Ebstein anomaly** (displacement of the septal and posterior, but not the anterior, leaflets into the RV), tricuspid valve prolapse, carcinoid plaque formation, collagen disease inflammation, valvular tumors, or tricuspid endocarditis. In addition, pacemaker lead valvular injury is an increasingly frequent iatrogenic cause.

Clinical Findings

A. Symptoms and Signs

The symptoms and signs of tricuspid regurgitation are identical to those resulting from RV failure due to any cause. As a generality, the diagnosis can be made by careful inspection of the JVP. The JVP waveform should decline during ventricular systole (the *x* descent). The timing of this decline can be observed by palpating the opposite carotid artery. As tricuspid regurgitation worsens, more and more of this *x* descent valley in the JVP is filled with the regurgitant wave until all of the *x* descent is obliterated and a positive systolic waveform will be noted in the JVP. An associated tricuspid regurgitation murmur may or may not be audible and can be distinguished from mitral regurgitation by the left parasternal location and an increase with inspiration (**Carvallo sign**). An S_3 may accompany the murmur and is related to the high flow returning to the RV from the RA. Cyanosis may be present if the increased RA pressure stretches the atrial septum and opens a PFO or there is a true ASD (eg, in about 50% of patients with Ebstein anomaly). Severe tricuspid regurgitation results in hepatomegaly, edema, and ascites.

B. Diagnostic Studies

The ECG is usually nonspecific, though atrial flutter or atrial fibrillation is common. The chest radiograph may reveal evidence of an enlarged RA or dilated azygous vein and pleural effusion. The echocardiogram helps assess severity of tricuspid regurgitation (criteria available in the 2014 AHA/ACC valvular heart disease guidelines). In addition, echocardiography/Doppler provides RV systolic pressure as well as RV size and function. A paradoxically moving interventricular septum may be present due to the volume overload on the RV. Catheterization confirms the presence of the regurgitant wave in the RA and elevated RA pressures. If the PA or RV systolic pressure is less than 40 mm Hg, primary valvular tricuspid regurgitation should be suspected. In addition, in patients with severe tricuspid regurgitation and ascites, a hepatic wedge pressure can be performed at the time of the right heart catheterization. If there is a high gradient between the mean RA pressure and mean hepatic wedge, then cirrhosis is likely present. Normally, the gradient across the liver is less than 5 mm Hg. Mild cirrhosis is suspected if gradient is 5–10 mm Hg, moderate disease if 10–15 mm Hg, and significant cirrhosis if greater than 15 mm Hg.

Treatment & Prognosis

Mild tricuspid regurgitation is common and generally can be well managed with diuretics. When severe tricuspid regurgitation is present, bowel edema may reduce the effectiveness of diuretics, such as furosemide, and intravenous diuretics should be used initially. Torsemide or bumetanide is better absorbed in this situation when oral diuretics are added. Aldosterone antagonists have a role as well, particularly if ascites is present. At times, the efficacy of loop diuretics can be enhanced by adding a thiazide diuretic (see Treatment, Heart Failure).

Since most tricuspid regurgitation is secondary, definitive treatment usually requires elimination of the cause of the RV dysfunction. Surgical valve replacement in secondary (functional) tricuspid regurgitation is rarely if ever indicated until the cause of the RV dysfunction is resolved. If the problem is left heart disease, then treatment of the left heart issues may lower pulmonary pressures, reduce RV size, and resolve the tricuspid regurgitation. Treatment for primary and secondary causes of pulmonary hypertension will generally reduce the tricuspid regurgitation. Guidelines suggest that tricuspid valve surgery may be considered when the tricuspid annular dilation at end-diastole exceeds 4.0 cm and the patient is symptomatic. It is a class I recommendation that tricuspid annuloplasty be performed when significant tricuspid regurgitation is present and mitral valve replacement or repair is being performed for mitral regurgitation. Annuloplasty without insertion of a prosthetic ring (**DeVega annuloplasty**) may also be effective in reducing the tricuspid annular dilation. The valve leaflet itself can occasionally be primarily repaired in tricuspid valve endocarditis. If there is an inherent defect in the tricuspid valve apparatus that cannot be repaired, then replacement of the tricuspid valve is warranted. A bioprosthetic valve rather than a mechanical valve, is almost always used because the risk of mechanical valve thrombosis is increased if the INR is not stable. Anticoagulation is *not* required for bioprosthetic valves unless there is associated atrial fibrillation or flutter. Tricuspid regurgitation due to bioprosthetic degeneration has been shown to respond to transcatheter valve replacement. There are early reports of percutaneous tricuspid valve replacement for native valve tricuspid regurgitation being successful.

When to Refer

- Anyone with moderate or severe tricuspid regurgitation should be seen at least once by a cardiologist to determine whether studies and intervention are needed.
- Severe tricuspid regurgitation requires regular follow-up by a cardiologist.

Axtell AL et al. Surgery does not improve survival in patients with isolated severe tricuspid regurgitation. J Am Coll Cardiol. 2019;74:715. [PMID: 31071413]
Hahn RT et al. Anatomic relationship of the complex tricuspid valve, right ventricle, and pulmonary vasculature: a review. JAMA Cardiol. 2019;4:478. [PMID: 30994879]

PULMONARY VALVE REGURGITATION

ESSENTIALS OF DIAGNOSIS

- Most cases are due to pulmonary hypertension resulting in high-pressure pulmonary valve regurgitation.
- Echocardiogram is definitive in high-pressure but may be less definitive in low-pressure pulmonary valve regurgitation.
- Low-pressure pulmonary valve regurgitation is well tolerated.

General Considerations

Pulmonary valve regurgitation can be divided into **high-pressure causes** (due to pulmonary hypertension) and **low-pressure causes** (usually due to a dilated pulmonary annulus, a congenitally abnormal [bicuspid or dysplastic] pulmonary valve, plaque from carcinoid disease, surgical pulmonary valve replacement, or the residual physiology following a surgical transannular patch used to reduce the outflow gradient in tetralogy of Fallot). Because the RV tolerates a volume load better than a pressure load, it tends to tolerate low-pressure pulmonary valve regurgitation for long periods of time without dysfunction.

Clinical Findings

Most patients are asymptomatic. Those with marked pulmonary valve regurgitation may exhibit symptoms of right heart volume overload. On examination, a hyperdynamic RV can usually be palpated (RV lift). If the PA is enlarged, it also may be palpated along the left sternal border. P_2 will be palpable in pulmonary hypertension and both systolic and diastolic thrills are occasionally noted. On auscultation, the second heart sound may be widely split due to prolonged RV systole or an associated right bundle branch block. A pulmonary valve systolic click may be noted as well as a right-sided gallop. If pulmonic stenosis is also present, the ejection click may decline with inspiration, while any associated systolic pulmonary murmur will increase. In high-pressure pulmonary valve regurgitation, the pulmonary diastolic (**Graham Steell**) murmur is readily audible. It is often contributed to by a dilated pulmonary annulus. The murmur increases with inspiration and diminishes with the Valsalva maneuver. In low-pressure pulmonary valve regurgitation, the PA diastolic pressure may be only a few mm Hg higher than the RV diastolic pressure, and there is little diastolic gradient to produce a murmur or characteristic echocardiography/Doppler findings. At times, only contrast angiography or MRI of the main PA will show the free-flowing pulmonary valve regurgitation in low-pressure pulmonary valve regurgitation. This situation is common in patients following repair of tetralogy of Fallot where, despite little murmur, there may effectively be no pulmonary valve present. This can be suspected by noting an enlarging right ventricle.

The ECG is generally of little value, although right bundle branch block is common, and there may be ECG criteria for RVH. The chest radiograph may show only the enlarged RV and PA. Echocardiography may demonstrate evidence of RV volume overload (paradoxical septal motion and an enlarged RV), and Doppler can determine peak systolic RV pressure and reveal any associated tricuspid regurgitation. The interventricular septum may appear flattened if there is pulmonary hypertension. The size of the main PA can be determined and color flow Doppler can demonstrate the pulmonary valve regurgitation, particularly in the high-pressure situation. Cardiac MRI and CT can be useful for assessing the size of the PA, for estimating regurgitant flow, for excluding other causes of pulmonary hypertension (eg, thromboembolic disease, peripheral PA stenosis), and for evaluating RV function. Cardiac catheterization is confirmatory only.

Treatment & Prognosis

Pulmonary valve regurgitation rarely needs specific therapy other than treatment of the primary cause. In low-pressure pulmonary valve regurgitation due to surgical transannular patch repair of tetralogy of Fallot, pulmonary valve replacement may be indicated if RV enlargement or dysfunction is present. In tetralogy of Fallot, the QRS will widen as RV function declines (a QRS greater than 180 msec, among other features, suggests a higher risk for sudden death) and increasing RV volumes should trigger an evaluation for potential severe pulmonary valve regurgitation. In carcinoid heart disease, pulmonary valve replacement with a porcine bioprosthesis may be undertaken, though the plaque from this disorder eventually coats the prosthetic pulmonary valve, limiting the life span of these valves. In high-pressure pulmonary valve regurgitation, treatment to control the cause of the pulmonary hypertension is key. High-pressure pulmonary valve regurgitation is poorly tolerated and is a serious condition that needs a thorough evaluation for cause and choice of therapy. Pulmonary valve replacement requires a bioprosthetic valve in most cases. Pulmonary valve regurgitation due to an RV to PA conduit or due to a pulmonary autograft replacement as part of the Ross procedure can be repaired with a percutaneous pulmonary valve (Melody valve). Bioprosthetic pulmonary valve regurgitation has also been treated using a percutaneous valve (Edwards Sapien). When the

pulmonary valve is replaced percutaneously, the PA is often stented open to provide a platform for the percutaneous valve.

When to Refer

- Patients with pulmonary valve regurgitation that results in RV enlargement should be referred to a cardiologist regardless of the estimated pulmonary pressures.

MANAGEMENT OF ANTICOAGULATION FOR PATIENTS WITH PROSTHETIC HEART VALVES

The risk of thromboembolism is much lower with bioprosthetic valves than mechanical prosthetic valves. Mechanical mitral valve prostheses also pose a greater risk for thrombosis than mechanical aortic valves. For that reason, **the INR should be kept between 2.5 and 3.5 for mechanical mitral prosthetic valves but can be kept between 2.0 and 2.5 for most mechanical aortic prosthetic valves.** If there are additional risk factors in patients with a mechanical AVR (atrial fibrillation, previous thromboembolism, LV dysfunction, hypercoagulable state, or presence of older valve such as a ball-in-cage), then the INR for a mechanical AVR should be similar to a mechanical mitral valve replacement. Guidelines currently suggest the following as well: (1) a recommendation (class IIa) to expand the use of vitamin K antagonists (VKAs), such as warfarin, for up to 6 months after initial bioprosthetic valve replacement; (2) a lower target INR of 1.5–2.0 for a mechanical AVR using the On-X valve (class IIb); and (3) a consideration of VKA use with an INR of 2.5 for at least 3 months after TAVR (class IIa). Data from 2018 suggest that antiplatelet medications are inferior to warfarin for the prevention of thrombus in patients with the On-X mechanical valve. Concern regarding thrombus formation on bioprosthetic valves (including TAVR valves) also led to a class I recommendation to use multimodality imaging to identify such thrombus (class I). The DOAC rivaroxaban has *not* been found to prevent stroke related to emboli from TAVR and it should not be used. It is acceptable, though, to use DOACs for the treatment of atrial fibrillation in patients with bioprosthetic valves. For patients with a TAVR valve, it is reasonable to use dual antiplatelet therapy (clopidogrel and aspirin) for 3–6 months after the procedure. After that, lifelong low-dose aspirin should be used. As noted earlier, using warfarin for at least 3 months after TAVR is reasonable (class IIb), although that practice is widely variable. Randomized trials have not shown a benefit with DOACs after TAVR.

The European Registry of Pregnancy and Cardiac Disease (ROPAC) reported on a registry that compared pregnant women who had undergone mechanical and bioprosthetic valve replacement to pregnant women who had not. Maternal mortality was similar between the mechanical and bioprosthetic valve patients (1.5% and 1.4%, respectively) but was much higher than those without an artificial valve (0.2%). When patients with either mechanical or bioprosthetic valves were further assessed, it was found that pregnant women with mechanical valves were more likely to suffer adverse events than women with bioprosthetic valves. Hemorrhagic events occurred in 23.1% versus 9.2%, miscarriage on warfarin occurred in 28.6% versus 9.2%, and late fetal death was noted in 7.1% versus 0.7%, respectively. These data suggest **a high risk for mortality and morbidity for pregnant patients with mechanical heart valves,** and in the WHO Classification of Maternal Cardiac Risk, the presence of a mechanical valve is considered a class III (out of IV) risk for pregnancy complications.

Stoppage of warfarin for noncardiac surgery is likewise dependent on which mechanical valve is involved, the patient-specific risk factors, and the procedure contemplated. The risk of thromboembolism is highest in the first few months after valve replacement. While the interruption of warfarin therapy is generally safe, most cases of valve thrombosis occur during periods of inadequate anticoagulation, so the time interval without coverage should be kept as short as possible. High-risk features include atrial fibrillation, a prior history of thromboembolism, heart failure or low LVEF, a hypercoagulable state, a mechanical valve in the mitral position, a known high-risk valve (ball-in-cage), or concomitant hypercoagulable state (such as with an associated cancer). The use of bridging VKAs, unfractionated heparin, low-molecular-weight heparin (LMWH), and antifibrinolytics in various clinical situations in patients with valvular heart disease is summarized in Table 10–4. In general, low-risk procedures (eg, pacemaker implantation, cataract removal, and routine dental work) require no stoppage of VKAs, while in other situations the warfarin can be stopped 3 days ahead of the procedure and resumed the night after the procedure (ie, in patients with bileaflet aortic valves) without any bridging unfractionated heparin or LMWH. It is reasonable to consider bridging based on the CHA2DS2-VASc score in patients with bioprosthetic heart valves or annuloplasty rings who take anticoagulants for atrial fibrillation. In high-risk patients, principally just those with a mechanical mitral valve, the warfarin should be stopped and *bridging with either unfractionated heparin or LMWH* begun once the INR falls below therapeutic levels. Fresh frozen plasma or prothrombin complex concentrate is reasonable in an emergency situation for acute reversal if serious bleeding occurs. Most patients with a mechanical valve should not have the warfarin reversed with vitamin K, if it can be avoided, because this can result in a transient hypercoagulable state, and it may take many days to reach a therapeutic INR again.

Warfarin causes fetal skeletal abnormalities in up to 2% of women who become pregnant while taking the medication, so every effort is made to defer mechanical valve replacement in women until after childbearing age. However, if a woman with a mechanical valve becomes pregnant while taking warfarin, the risk of stopping warfarin may be higher for the mother than the risk of continuing warfarin for the fetus. The risk of warfarin to the fetal skeleton is greatest during the first trimester and, remarkably, is more related to dose than to the INR level. Guidelines suggest it is reasonable to continue warfarin for the first trimester if the dose is 5 mg/day or less. If the dose is more than 5 mg/day, it is appropriate to consider either LMWH (as long as the anti-Xa is being monitored [range: 0.8 units/mL

Table 10–4. Recommendations for administering vitamin K antagonist (VKA) therapy in patients undergoing procedures or patients with certain clinical conditions.

Procedures	Recommendations
General	Stop VKA 5 days prior and resume 12–24 hours after procedure
Bridging for mechanical heart valves	Required only for those at high risk for thromboembolism (generally only those with a mechanical mitral [not aortic] valve) Bridge with UFH or LMWH and stop UFH 4–6 hours before procedure or stop LMWH 24 hours before procedure Resume 48–72 hours after the procedure
Clinical Situations	**Recommendations**
Atrial fibrillation and moderate or severe mitral stenosis	VKA (target INR 2.0–3.0) If patient refuses, aspirin (50–100 mg) plus clopidogrel (75 mg)
Sinus rhythm and mitral stenosis	If left atrial size > 5.5 cm, then consider VKA (target 2.0–3.0)
Intermittent atrial fibrillation or history of systemic embolus and mitral stenosis	VKA (target INR 2.0–3.0)
Endocarditis	
Native valve or bioprosthetic valve endocarditis	No anticoagulation recommended
Mechanical valve endocarditis	Hold VKA until "safe to resume" (generally when mycotic aneurysm is ruled out or there is no need for urgent surgery)
Aspirin use in patients with a bioprosthetic valve	
Bioprosthetic aortic or mitral valve replacement	Aspirin (50–100 mg) indefinitely
Transcatheter valve replacement	Aspirin (50–100 mg) indefinitely plus clopidogrel (75 mg) for first 6 months. Reasonable to consider VKA to achieve INR 2.5 for first 3 months
Mitral or aortic repair	Aspirin (50–100 mg) indefinitely
Long-term anticoagulation after valve replacement	
Bioprosthetic valve in normal sinus rhythm	Aspirin (50–100 mg). Anticoagulation with a VKA to achieve an INR of 2.5 is reasonable for at least 3 months and up to 6 months after surgical MVR or AVR in patients at low risk for bleeding
Mechanical valve replacement	VKA (target INR 2.0–3.0 for mechanical aortic valve, target INR 1.5–2.5 for On-X aortic valve, target INR 2.5–3.5 for mechanical mitral valve) plus aspirin (50–100 mg)
Prosthetic valve thrombosis	
Right-sided valve	Slow infusion fibrinolytic therapy or intravenous heparin
Left-sided valve	Early surgery if thrombus large (> 0.8 cm^2), symptomatic from valvular obstruction, high surgical risk, or LA thrombus. Thrombolysis with heparin or slow-infusion fibrinolytic therapy may be tried initially if patient is stable If thrombus evident on bioprosthetic valve creating increased gradient, use of VKA reasonable to assess whether obstructive gradient can be improved
Pregnancy and a mechanical heart valve	Add aspirin (50–100 mg) for high risk VKA may be used during first trimester and throughout pregnancy if dose of warfarin is ≤ 5 mg/day If VKA dosage normally > 5 mg/day, then adjusted dose LMWH twice daily throughout pregnancy (follow anti-Xa 4 hours after dose, with target of 0.8 units/mL to 1.2 units/mL) or LMWH may be used only during the first trimester, then resume VKA during second and third trimesters ***or*** Adjusted dose UFH every 12 hours throughout pregnancy (aPTT > 2 times control) or UFH may be used only during the first trimester, then resume VKA during second and third trimester Discontinuation of VKA with initiation of UFH (2 times normal PTT) recommended before planned vaginal delivery

aPTT, activated partial thromboplastin time; AVR, aortic valve replacement; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MVR, mitral valve replacement; PTT, partial thromboplastin time. UFH, unfractionated heparin.
Adapted from Nishimura RA et al. 2014 AHA/ACC guidelines for the management of patients with valvular heart disease: executive summary. Circulation. 2014;129:2440–92; and Nishimura RA et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2017;70:252–289.

to 1.2 units/mL 4–6 hours post-dose]) or continuous intravenous unfractionated heparin (if the activated partial thromboplastin time [aPTT] can be monitored and is at least two times control). Guidelines suggest warfarin and low-dose aspirin are safe during the second and third trimester, and then should be stopped upon anticipation of delivery. At time of vaginal delivery, unfractionated intravenous heparin with aPTT at least two times control is desirable. DOACs (antithrombin or Xa inhibitors) should *not* be used in place of warfarin for mechanical prosthetic valves since there are no data that they are safe during pregnancy or safe for mechanical valves in general.

Management of suspected mechanical valve thrombosis depends on whether a left-sided or right-sided valve is involved, the size of the thrombus, and the patient's clinical condition. Simple fluoroscopy can help assess mechanical valve motion, although a TEE is indicated to assess thrombus size. **Therapeutic unfractionated heparin should be given to all patients with a thrombosed valve,** and this alone is generally effective. Fibrinolytic therapy is indicated if heparin therapy is ineffective and the clinical onset has been less than 2 weeks, the thrombus is smaller than 0.8 cm^2, New York Heart Association (NYHA) class symptoms are mild (functional class I or II), or the valve is right-sided. Surgery is rarely indicated; it is reserved for those with left-sided mechanical valves in NYHA functional class III or IV heart failure or in whom TEE demonstrates a mobile thrombus larger than 0.8 cm^2. The use of urgent initial therapy for a thrombosed mechanical valve should include low-dose, slow-infusion fibrinolytic therapy or urgent surgery if the patient is symptomatic.

Arya R. Pregnancy outcomes in women with mechanical prosthetic heart valves. Thromb Res. 2019;181:S37. [PMID: 31477226]

CORONARY HEART DISEASE (Atherosclerotic CAD, Ischemic Heart Disease)

CHD, or atherosclerotic CAD, is the number one cause of death in the United States and worldwide. Every minute in the United States, a person dies of CHD. About 37% of people who experience an acute coronary event, either angina or MI, will die of it in the same year. Death rates of CHD have declined every year since 1968, with about half of the decline from 1980 to 2000 due to treatments and half due to improved risk factors. CHD is still responsible for 1 in 4 of all deaths in the United States, totaling over 659,000 deaths annually. Each year, 805,000 individuals have a heart attack in the United States. CHD afflicts nearly 18.2 million Americans, and the prevalence rises steadily with age; thus, the aging of the US population promises to increase the overall burden of CHD.

Risk Factors for CAD

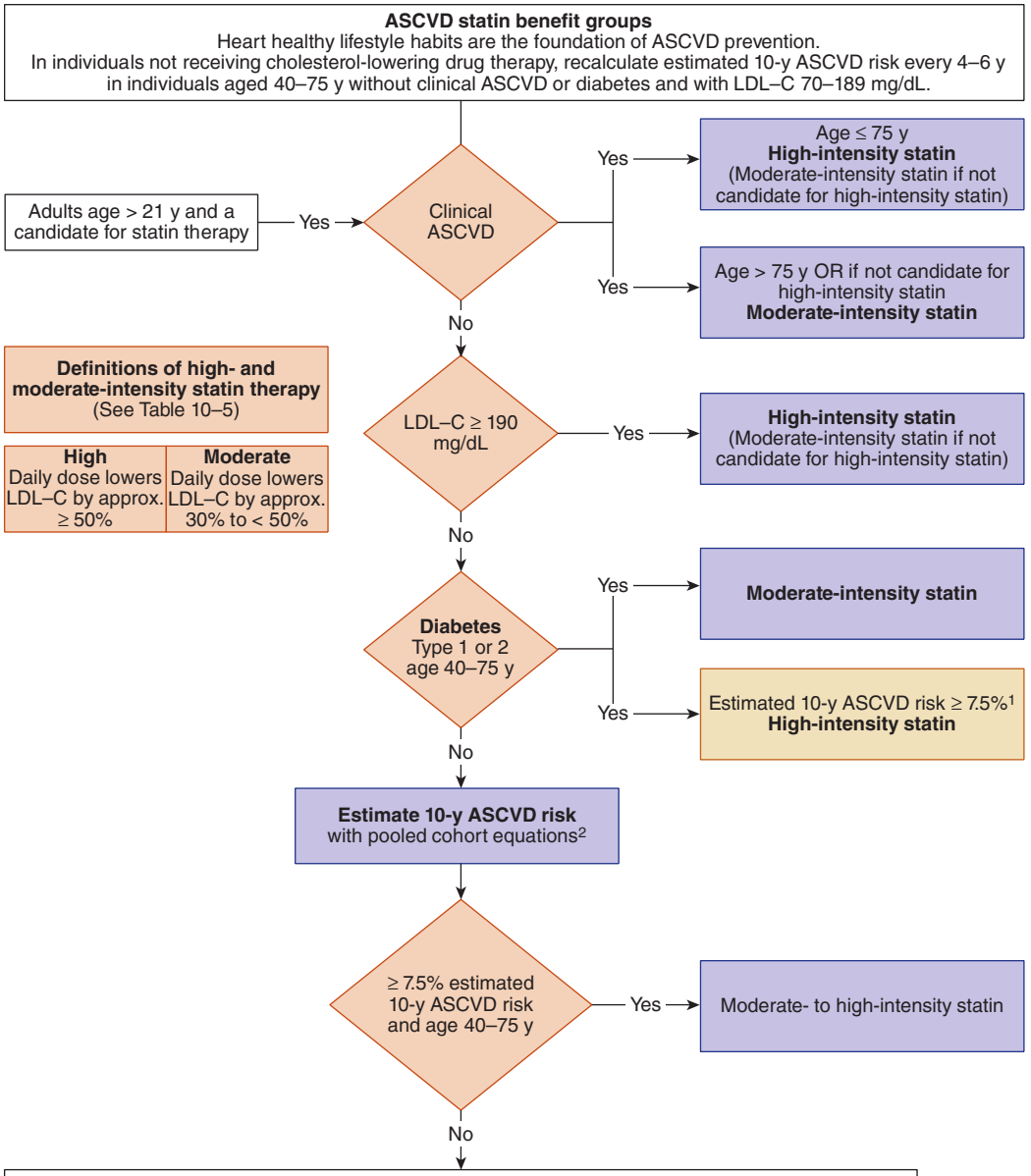
Most patients with CHD have some identifiable risk factor. These include a **positive family history** (the younger the onset in a first-degree relative, the greater the risk), **male sex, blood lipid abnormalities, diabetes mellitus, hypertension, physical inactivity, abdominal obesity, cigarette smoking, psychosocial factors,** and consumption of **too few fruits and vegetables** and **too much alcohol**. Many of these risk factors are modifiable. **Smoking remains the number one preventable cause of death and illness in the United States.** Although cigarette smoking rates have declined in the United States in recent decades, 12% of women and 15.6% of men still smoke. According to the World Health Organization, 1 year after quitting, the risk of CHD decreases by 50%. Various interventions have been shown to increase the likelihood of successful smoking cessation (see Chapter 1).

Hypercholesterolemia is an important modifiable risk factor for CHD. Risk increases progressively with higher levels of LDL cholesterol and declines with higher levels of HDL cholesterol. Composite risk scores, such as the Framingham score and the 10-year atherosclerotic CVD risk calculator (http://my.americanheart.org/cvriskcalculator), provide estimates of the 10-year probability of development of CHD that can guide primary prevention strategies. The 2018 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults suggests statin therapy in four populations: patients with (1) clinical atherosclerotic disease, (2) LDL cholesterol 190 mg/dL or higher, (3) diabetes who are aged 40–75 years, and (4) an estimated 10-year atherosclerotic risk of 7.5% or more aged 40–75 years (Figure 10–7). Importantly, *the guidelines do not recommend treating to a target LDL cholesterol.* Patients in these categories should be treated with a moderate- or high-intensity statin, with high-intensity statin for the higher-risk populations (Table 10–5). The ACC/AHA atherosclerotic CVD estimator allows clinicians to determine the 10-year CHD risk to determine treatment decisions (http://tools.acc.org/ascvd-risk-estimator-plus/).

The **metabolic syndrome** is defined as a constellation of three or more of the following: abdominal obesity, triglycerides 150 mg/dL or higher, HDL cholesterol less than 40 mg/dL for men or less than 50 mg/dL for women, fasting glucose 110 mg/dL or higher, and hypertension. This syndrome is increasing in prevalence at an alarming rate. Related to the metabolic syndrome, the epidemic of **obesity** in the United States is likewise a major factor contributing to CHD risk.

Myocardial Hibernation & Stunning

Areas of myocardium that are persistently underperfused but still viable may develop sustained contractile dysfunction. This phenomenon, which is termed **myocardial hibernation,** appears to represent an adaptive response that may be associated with depressed LV function. It is important to recognize this phenomenon, since this form of dysfunction is reversible following coronary revascularization. Hibernating myocardium can be identified by radionuclide testing, PET, contrast-enhanced MRI, or its retained response to inotropic stimulation with dobutamine. A related phenomenon, termed **myocardial stunning,** is the occurrence of persistent contractile dysfunction following prolonged or repetitive episodes of myocardial



[1]Percent reduction in LDL–C can be used as an indication of response and adherence to therapy but is not in itself a treatment goal.

[2]The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx.

[3]Primary LDL–C ≥ 160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset < 55 years of age in a first-degree male relative or < 65 years of age in a first-degree female relative, high-sensitivity C-reactive protein > 2 mg/L, CAC score ≥ 300 Agatston units or ≥ 75 percentile for age, sex, and ethnicity, ankle-brachial index < 0.9, or elevated lifetime risk of ASCVD.

▲ **Figure 10–7.** Major recommendations for statin therapy for atherosclerotic CVD prevention. ASCVD, atherosclerotic CVD; CAC, coronary artery calcium; LDL–C, LDL cholesterol. (Adapted from Stone NJ et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1.)

Table 10–5. High-, moderate-, and low-intensity statin therapy.[1,2,3]

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
LDL–C lowering[4] ≥ 50%	LDL–C lowering[4] 30% to 49%	LDL-C lowering[4] < 30%
Atorvastatin (40 mg[5]) 80 mg **Rosuvastatin 20 mg (40 mg)**	**Atorvastatin 10 mg** (*20 mg*) **Rosuvastatin** (*5 mg*) **10 mg** **Simvastatin 20–40 mg[6]** **Pravastatin 40 mg** (*80 mg*) **Lovastatin 40 mg** (*80 mg*) *Fluvastatin XL 80 mg* **Fluvastatin 40 mg twice daily** *Pitavastatin 1–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg*

[1]Percent LDL-C reductions with the primary statin medications used in clinical practice (atorvastatin, rosuvastatin, simvastatin) were estimated using the median reduction in LDL-C from the VOYAGER database.S3.2.1-2 Reductions in LDL-C for other statin medications (fluvastatin, lovastatin, pitavastatin, pravastatin) were identified according to FDA-approved product labeling in adults with hyperlipidemia, primary hypercholesterolemia, and mixed dyslipidemia.
[2]**Boldface type** indicates specific statins and doses that were evaluated in RCTs, and the Cholesterol Treatment Trialists' 2010 meta-analysis. All these RCTs demonstrated a reduction in major cardiovascular events.
[3]Percent reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice.
[4]LDL-C lowering that should occur with the dosage listed below.
[5]Evidence from one RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL study.
[6]Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.
IDEAL, Incremental Decrease through Aggressive Lipid Lowering study; LDL–C, low-density lipoprotein cholesterol; RCTs, randomized controlled trials.
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ischemia. Clinically, myocardial stunning is often seen after reperfusion of acute MI and is defined with improvement following revascularization.

Creamer MR et al. Tobacco product use and cessation indicators among adults—United States, 2018. MMWR Morb Mortal Wkly Rep. 2019;68:1013. [PMID: 31725711]
Virani SS et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. Circulation. 2021;143:e254. [PMID: 33501848]

Primary & Secondary Prevention of CHD

Although many risk factors for CHD are not modifiable, it is now clear that interventions, such as smoking cessation, treatment of dyslipidemia, and lowering of BP can both prevent coronary disease and delay its progression and complications after it is manifest.

Lowering LDL levels delays the progression of atherosclerosis and in some cases may produce regression. Even in the absence of regression, fewer new lesions develop, endothelial function may be restored, and coronary event rates are markedly reduced in patients with clinical evidence of vascular disease.

A series of clinical trials has demonstrated the efficacy of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in preventing death, coronary events, and strokes. Beneficial results have been found in patients who have already experienced coronary events (secondary prevention), those at particularly high risk for events (patients with diabetes and patients with peripheral artery disease), those with elevated cholesterol without multiple risk factors, and those without vascular disease or diabetes with elevated high-sensitivity CRP (hsCRP) with normal LDL levels. The benefits of statin therapy at moderate and high doses (Table 10–5) are recommended by the cholesterol treatment guidelines. The IMPROVE-IT study showed that ezetimibe, 10 mg daily, combined with simvastatin was modestly better than simvastatin alone in reducing the risk of MI and ischemic stroke, but not mortality, in stabilized patients following an acute coronary syndrome. This was associated with a reduction of LDL to 53.7 mg/dL compared to 69.7 mg/dL. With this data, ezetimibe can be used in combination with statin therapy in patients who are not at target cholesterol level for secondary prevention (for individuals at high risk for cardiovascular events with an LDL > 70 on maximal intensity statin therapy [IIa recommendation]) or cannot tolerate high-dose statin therapy.

Benefits occurred regardless of age, race, baseline cholesterol levels, or the presence of hypertension. It is clear that for patients with vascular disease, statins provide benefit for those with normal cholesterol levels, and that more aggressive statin use is associated with greater benefits. **All patients at significant risk for vascular events should**

receive a statin regardless of their cholesterol levels, and many experts recommend that with those who have prior cardiovascular events should have their LDL lowered below 70 mg/dL.

Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) reduce LDL cholesterol levels significantly beyond levels associated with traditional statin therapy. These therapies have been studied in randomized trials of patients with maximally tolerated statin therapy (and for patients with statin intolerance) and have lowered LDL with signals of improved cardiovascular outcomes. The FOURIER trial showed that the PCSK9 inhibitor evolocumab, on top of statin, reduced the composite of atherothrombotic outcomes by 20% but did not reduce mortality. The ODYSSEY Outcomes trial demonstrated alirocumab reduced cardiovascular events in patients with acute coronary syndromes. Alirocumab and evolocumab have been approved by the FDA for patients on maximally tolerated statin therapy with familial hypercholesterolemia and atherosclerotic vascular disease, or both, and who require additional lowering of LDL. These medications cost several thousand dollars per year in the United States. Alirocumab has also been approved by the FDA for secondary prevention of cardiovascular events. Inclisiran (a small interfering RNA that goes to the liver and prevents the production of PCSK9) has been studied as a twice yearly injection showing reduction in LDL. The therapy was approved by the FDA in early 2022.

While fish oil supplements have *not* been shown to provide benefit for reducing risk, icosapent ethyl, a concentrated eicosapentaenoic acid at a high dose, was shown to be beneficial in the REDUCE-IT trial. Patients with established CVD or with diabetes and other risk factors, with fasting triglyceride level of 135–499 mg/dL, who were on statins were randomized to 2 g of icosapent ethyl twice daily or placebo. There was a 26% relative risk reduction in cardiovascular death, MI, and stroke, as well as a 20% relative risk reduction in cardiovascular death. Icosapent ethyl is approved by the FDA as an adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, or unstable angina requiring hospitalization in patients with triglycerides of 150 mg/dL or more and either established CVD or diabetes mellitus and two or more additional risk factors. The role of high-dose omega-3 fatty acids was studied compared to corn oil and not shown to reduce cardiovascular events, leading to increased interest in comparative studies.

Treatment to raise HDL levels has failed to show benefit. The AIM High trial found no benefit from the addition of niacin in patients with vascular disease and a serum LDL near 70 mg/dL who were receiving statin therapy. The HPS2-THRIVE trial found no benefit but rather substantial harm of extended-release niacin (2 g) plus laropiprant (an antiflushing agent) for preventing vascular events in a population of over 25,000 patients with vascular disease who were taking simvastatin.

For *primary* prevention, aspirin has little overall benefit, including for patients with established diabetes, and is not recommended for most patients. In October 2021, the USPSTF issued guidance on the use of aspirin for primary prevention of cardiovascular events. The document recommended that patient ages 40–49 should have a shared-decision making conversation regarding the potential risk and benefits of initiating aspirin therapy for primary prevention. In addition, the document recommended that patients 60 years of age and older should not initiate aspirin for primary prevention of CVD.

Antiplatelet therapy is a very effective measure for *secondary* prevention and patients with established vascular disease should be treated with aspirin. The exact dose of aspirin in chronic CAD (81 mg vs 325 mg) was evaluated in a large pragmatic trial (ADAPTABLE). The unique pragmatic clinical trial design demonstrated that 81 mg aspirin was associated with a favorable cardiovascular event risk and bleeding risk compared with 325 mg daily.

While clopidogrel was found to be effective at preventing vascular events for 9–12 months after acute coronary syndromes, and there are some benefits in prolonging dual antiplatelet therapy after coronary stenting, clopidogrel was *not* found to be effective at preventing vascular events in combination with aspirin with longer-term treatment in the CHARISMA trial. This trial included patients with clinically evident stable atherothrombosis or with multiple risk factors; all were treated with aspirin and observed for a median of 28 months.

In the COMPASS trial, rivaroxaban, a direct factor Xa inhibitor, at a dose of 2.5 mg twice daily in addition to 100 mg of aspirin, was shown to reduce cardiovascular death, MI, and stroke by a relative risk reduction of 24% compared to 100 mg aspirin monotherapy in stable patients with CAD and peripheral artery disease. Bleeding was modestly increased. All-cause mortality was also reduced by 18%. This regimen is approved by the FDA and is used for long-term management of patients with CAD and peripheral artery disease and should be considered in this group at high risk for adverse cardiac events with a low bleeding risk profile.

The HOPE and the EUROPA trials demonstrated that ACE inhibitors (ramipril 10 mg/day and perindopril 8 mg/day, respectively) reduced fatal and nonfatal vascular events (cardiovascular deaths, nonfatal MIs, and nonfatal strokes) by 20–25% in patients at high risk, including patients with diabetes with additional risk factors or patients with clinical coronary, cerebral, or peripheral arterial atherosclerotic disease. An overview of these trials has demonstrated that while low-risk patients may *not* derive substantial benefits from ACE inhibitors, **most patients with vascular disease, even in the absence of heart failure or LV dysfunction, should be treated with an ACE inhibitor.**

Over one-third of patients with vascular disease have type 2 diabetes. In addition to controlling risk factors, using high-intensity statins and ACE inhibitors or ARBs, **there is proven benefit to reduce cardiovascular events by using oral sodium–glucose cotransporter 2 (SGLT2) inhibitors (specifically, empagliflozin, dapagliflozin, or canagliflozin) or injectable GLP1-receptor agonists (liraglutide, semaglutide, dulaglutide).** The cardiovascular benefits appear to be independent from the modest glucose

lowering effects, and SGLT2 inhibitors have benefits for patients with heart failure regardless of whether they have diabetes (see Heart Failure section). In addition, newer data demonstrate the cardiovascular outcome benefits in patients with both heart failure with reduced EF and heart failure with preserved EF.

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CHRONIC STABLE ANGINA PECTORIS (Chronic Coronary Syndromes)

ESSENTIALS OF DIAGNOSIS

- Precordial chest pain, usually precipitated by stress or exertion, relieved rapidly by rest or nitrates.
- ECG or scintigraphic evidence of ischemia during pain or stress testing.
- Angiographic demonstration of significant obstruction of major coronary vessels.

General Considerations

Angina pectoris is the manifestation of stable CAD or chronic coronary syndromes, and it is usually due to atherosclerotic heart disease. Coronary vasospasm may occur at the site of a lesion or, less frequently, in apparently normal vessels. Other unusual causes of coronary artery obstruction, such as congenital anomalies, emboli, arteritis, or dissection may cause ischemia or infarction. Angina may also occur in the absence of coronary artery obstruction as a result of severe myocardial hypertrophy, severe aortic stenosis or regurgitation, or in response to increased metabolic demands, as in hyperthyroidism, marked anemia, or paroxysmal tachycardias with rapid ventricular rates.

Clinical Findings

A. Symptoms

The diagnosis of angina pectoris principally depends on the history, which should specifically include the following information: circumstances that precipitate and relieve angina, characteristics of the discomfort, location and radiation, duration of attacks, and effect of nitroglycerin.

1. Circumstances that precipitate and relieve angina— Angina occurs most commonly during activity and is relieved by resting. Patients may prefer to remain upright rather than lie down, as increased preload in recumbency increases myocardial work. The amount of activity required to produce angina may be relatively consistent under comparable physical and emotional circumstances or may vary from day to day. The threshold for angina is usually lower after meals, during excitement, or on exposure to cold. It is often lower in the morning or after strong emotion; the latter can provoke attacks in the absence of exertion. In addition, discomfort may occur during sexual activity, at rest, or at night as a result of coronary spasm.

2. Characteristics of the discomfort— Patients often do not refer to angina as "pain" but as a sensation of tightness, squeezing, burning, pressing, choking, aching, bursting, "gas," indigestion, or an ill-characterized discomfort. It is often characterized by clenching a fist over the mid chest. The distress of angina is rarely sharply localized and is not spasmodic.

3. Location and radiation— The distribution of the distress may vary widely in different patients but is usually the same for each patient unless unstable angina or MI supervenes. In most cases, the discomfort is felt behind or slightly to the left of the mid sternum. When it begins farther to the left or, uncommonly, on the right, it characteristically moves centrally substernally. Although angina may radiate to any dermatome from C8 to T4, it radiates most often to the left shoulder and upper arm, frequently moving down the inner volar aspect of the arm to the elbow, forearm, wrist, or fourth and fifth fingers. It may also radiate to the right shoulder or arm, the lower jaw, the neck, or even the back.

4. Duration of attacks— Angina is generally of short duration and subsides completely without residual discomfort. If the attack is precipitated by exertion and the patient promptly stops to rest, it usually lasts under 3 minutes. Attacks following a heavy meal or brought on by anger often last 15–20 minutes. Attacks lasting more than 30 minutes are unusual and suggest the development of an acute coronary syndrome with unstable angina, MI, or an alternative diagnosis.

5. Effect of nitroglycerin— The diagnosis of angina pectoris is supported if sublingual nitroglycerin promptly and invariably shortens an attack and if prophylactic nitrates permit greater exertion or prevent angina entirely.

B. Signs

Examination during angina frequently reveals a significant elevation in systolic and diastolic BP, although hypotension

may also occur, and may reflect more severe ischemia or inferior ischemia (especially with bradycardia) due to a **Bezold-Jarisch reflex**. Occasionally, a gallop rhythm and an apical systolic murmur due to transient mitral regurgitation from papillary muscle dysfunction are present during pain only. Supraventricular or ventricular arrhythmias may be present, either as the precipitating factor or as a result of ischemia.

It is important to detect signs of diseases that may contribute to or accompany atherosclerotic heart disease, eg, diabetes mellitus (retinopathy or neuropathy), xanthelasma tendinous xanthomas, hypertension, thyrotoxicosis, myxedema, or peripheral artery disease. Aortic stenosis or regurgitation, HCM, and mitral valve prolapse should be sought, since they may produce angina or other forms of chest pain.

C. Laboratory Findings

Other than standard laboratory tests to evaluate for acute coronary syndrome (troponin and CK-MB) and factors contributing to ischemia (such as anemia) and to screen for risk factors that may increase the probability of true CHD (such as hyperlipidemia and diabetes mellitus), blood tests are not helpful to diagnose chronic angina.

D. ECG

The resting ECG is often normal in patients with angina. In the remainder, abnormalities include old MI, nonspecific ST–T changes, and changes of LVH. During anginal episodes, as well as during asymptomatic ischemia, *the characteristic ECG change is horizontal or downsloping ST-segment depression that reverses after the ischemia disappears.* T wave flattening or inversion may also occur. Less frequently, transient ST-segment elevation is observed; this finding suggests severe (transmural) ischemia from coronary occlusion, and it can occur with coronary spasm.

E. Pretest Probability

The history as detailed above, the physical examination findings, and laboratory and ECG findings are used to develop a pretest probability of CAD as the cause of the clinical symptoms. Other important factors to include in calculating the pretest probability of CAD are patient age, sex, and clinical symptoms. Patients with low to intermediate pretest probability for CAD should undergo noninvasive stress testing whereas patients with high pretest probability are generally referred for cardiac catheterization. National review of diagnostic cardiac catheterization findings in patients without known CAD undergoing angiography has shown that between 38% and 40% of patients do not have obstructive disease.

F. Exercise ECG

Exercise ECG testing is the most commonly used noninvasive procedure for evaluating for inducible ischemia in the patient with angina. Exercise ECG testing is often combined with imaging studies (nuclear or echocardiography), but in low-risk patients without baseline ST-segment abnormalities or in whom anatomic localization is not necessary, the exercise ECG remains the recommended initial procedure because of considerations of cost, convenience, and longstanding prognostic data.

Exercise testing can be done on a motorized treadmill or with a bicycle ergometer. A variety of exercise protocols are utilized, the most common being the **Bruce protocol,** which increases the treadmill speed and elevation every 3 minutes until limited by symptoms. At least two ECG leads should be monitored continuously.

1. Precautions and risks—The risk of exercise testing is about one infarction or death per 1000 tests, but individuals who have pain at rest or minimal activity are at higher risk and should not be tested. **Many of the traditional exclusions, such as recent MI or heart failure, are no longer used if the patient is stable and ambulatory, but symptomatic aortic stenosis remains a relative contraindication.**

2. Indications—Exercise testing is used (1) to confirm the diagnosis of angina; (2) to determine the severity of limitation of activity due to angina; (3) to assess prognosis in patients with known coronary disease, including those recovering from MI, by detecting groups at high or low risk; and (4) to evaluate responses to therapy. Because false-positive tests often exceed true positives, leading to much patient anxiety and self-imposed or mandated disability, exercise testing of asymptomatic individuals should be done only for those whose occupations place them or others at special risk (eg, airline pilots).

3. Interpretation—The usual ECG criterion for a positive test is 1-mm (0.1-mV) horizontal or downsloping ST-segment depression (beyond baseline) measured 80 msec after the J point. By this criterion, 60–80% of patients with anatomically significant coronary disease will have a positive test, but 10–30% of those without significant disease will also be positive. False positives are uncommon when a 2-mm depression is present. Additional information is inferred from the time of onset and duration of the ECG changes, their magnitude and configuration, BP and heart rate changes, the duration of exercise, and the presence of associated symptoms. In general, patients exhibiting more severe ST-segment depression (more than 2 mm) at low workloads (less than 6 minutes on the Bruce protocol) or heart rates (less than 70% of age-predicted maximum)—especially when the duration of exercise and rise in BP are limited or when hypotension occurs during the test—have more severe disease and a poorer prognosis. Depending on symptom status, age, and other factors, such patients should be referred for coronary arteriography and possible revascularization. On the other hand, less impressive positive tests in asymptomatic patients are often "false positives." Therefore, exercise testing results that do not conform to the clinical suspicion should be confirmed by stress imaging.

G. Myocardial Stress Imaging

Myocardial stress imaging (scintigraphy, echocardiography, or MRI) is indicated (1) when the resting ECG makes

an exercise ECG difficult to interpret (eg, left bundle branch block, baseline ST–T changes, low voltage); (2) for confirmation of the results of the exercise ECG when they are contrary to the clinical impression (eg, a positive test in an asymptomatic patient); (3) to localize the region of ischemia; (4) to distinguish ischemic from infarcted myocardium; (5) to assess the completeness of revascularization following bypass surgery or coronary angioplasty; or (6) as a prognostic indicator in patients with known coronary disease. Published criteria summarize these indications for stress testing.

1. Myocardial perfusion scintigraphy—This test, also known as **radionuclide imaging,** provides images in which radionuclide uptake is proportionate to blood flow at the time of injection.

Stress imaging is positive in about 75–90% of patients with anatomically significant coronary disease and in 20–30% of those without it. Occasionally, other conditions, including infiltrative diseases (sarcoidosis, amyloidosis), left bundle branch block, and dilated cardiomyopathy, may produce resting or persistent perfusion defects. False-positive radionuclide tests may occur as a result of diaphragmatic attenuation or, in women, attenuation through breast tissue. Tomographic imaging (single-photon emission computed tomography [SPECT]) can reduce the severity of artifacts.

2. Radionuclide angiography—This procedure, also known as **multi-gated acquisition scan,** or **MUGA scan,** uses radionuclide tracers to image the LV and measures its EF and wall motion. In coronary disease, resting abnormalities usually represent infarction, and those that occur only with exercise usually indicate stress-induced ischemia. Exercise radionuclide angiography has approximately the same sensitivity as myocardial perfusion scintigraphy, but it is less specific in older individuals and those with other forms of heart disease. In addition, because of the precision around LVEF, the test is also used for monitoring patients exposed to cardiotoxic therapies (such as chemotherapeutic agents).

3. Stress echocardiography—Echocardiograms performed during supine exercise or immediately following upright exercise may demonstrate exercise-induced *segmental wall motion abnormalities* as an indicator of ischemia. In experienced laboratories, the test accuracy is comparable to that obtained with scintigraphy—though a higher proportion of tests is technically inadequate. While exercise is the preferred stress because of other information derived, pharmacologic stress with high-dose dobutamine (20–40 mcg/kg/minute) can be used as an alternative to exercise.

H. Other Imaging

1. Positron emission tomography—PET and SPECT scanning can accurately distinguish transiently dysfunctional ("stunned") myocardium from scar tissue.

2. CT and MRI scanning—CT scanning can image the heart and, with contrast medium and multislice technology, the coronary arteries. **Multislice CT angiography may be useful in evaluating patients with low likelihood of significant CAD to rule out disease.** Its use has been associated with lower 5-year mortality compared to standard care in patients with stable chest pain. With lower radiation exposure than radionuclide SPECT imaging, CT angiography may also be useful for evaluating chest pain and suspected acute coronary syndrome. In the large randomized comparative effectiveness PROMISE trial, patients with stable chest pain undergoing anatomic imaging with CT angiography had similar outcomes to patients undergoing functional testing (stress ECG, stress radionuclide, or stress echocardiography). CT angiography with noninvasive functional assessment of coronary stenosis (fractional flow reserve), termed **CT-FFR,** has also been evaluated in patients with low-intermediate likelihood of CAD. CT-FFR has been shown to reduce the number of patients without coronary disease requiring invasive angiography. CT-FFR has been approved for clinical use and is being used in clinical practice in the United States and Europe. The use of CT-FFR has been endorsed with a level IIa recommendation for intermediate risk patients with chest pain and no prior history of CAD with a 40–90% stenosis on CT imaging to guide need for revascularization in the 2021 ACC/AHA Guideline for the Evaluation and Diagnosis of Chest Pain.

Electron beam CT (EBCT) (Coronary Calcium Score) can quantify coronary artery calcification, which is highly correlated with atheromatous plaque and has high sensitivity, but low specificity, for obstructive coronary disease. This test has not traditionally been used in symptomatic patients. According to the AHA, persons who are at low risk (less than 10% 10-year risk) or at high risk (greater than 20% 10-year risk) for obstructive coronary disease do not benefit from coronary calcium assessment (class III, level of evidence: B). However, in clinically selected, intermediate-risk patients (5–7.5% atherosclerotic CVD), it may be reasonable to determine the atherosclerosis burden using EBCT in order to refine clinical risk prediction and to select patients for more aggressive target values for lipid-lowering therapies (class IIb, level of evidence: B).

Cardiac MRI using gadolinium provides high-resolution images of the heart and great vessels without radiation exposure or use of iodinated contrast media. Gadolinium has been associated with a rare but fatal complication in patients with severe kidney disease, called **necrotizing systemic fibrosis.** Gadolinium can demonstrate perfusion using dobutamine or adenosine to produce pharmacologic stress. Advances have been made in imaging the proximal coronary arteries. Perhaps the most clinically used indication of cardiac MRI is for identification of **myocardial fibrosis,** either from MI or infiltration, done with gadolinium contrast. This allows high-resolution imaging of myocardial viability and infiltrative cardiomyopathies.

I. Ambulatory ECG Monitoring

Ambulatory ECG recorders can monitor for ischemic ST-segment depression, but this modality is rarely used for ischemia detection. In patients with CAD, these episodes usually signify ischemia, even when asymptomatic ("silent").

J. Coronary Angiography

Selective coronary arteriography is the definitive diagnostic procedure for CAD. It can be performed with low mortality (about 0.1%) and morbidity (1–5%), but due to the invasive nature and cost, it is recommended only in patients with a high pretest probability of CAD.

Coronary arteriography should be performed in the following circumstances if percutaneous transluminal coronary angioplasty or bypass surgery is a consideration:

1. Life-limiting stable angina despite an adequate medical regimen.
2. Clinical presentation (unstable angina, postinfarction angina, etc) or noninvasive testing suggests high-risk disease (see Indications for Revascularization).
3. Concomitant aortic valve disease and angina pectoris, to determine whether the angina is due to accompanying coronary disease.
4. Asymptomatic older patients undergoing valve surgery so that concomitant bypass may be done if the anatomy is propitious.
5. Recurrence of symptoms after coronary revascularization to determine whether bypass grafts or native vessels are occluded.
6. Cardiac failure where a surgically correctable lesion, such as LV aneurysm, mitral regurgitation, or reversible ischemic dysfunction, is suspected.
7. Survivors of sudden death, symptomatic, or life-threatening arrhythmias when CAD may be a correctable cause.
8. Chest pain of uncertain cause or cardiomyopathy of unknown cause.
9. Emergently performed cardiac catheterization with intention to perform primary PCI in patients with suspected acute MI.

A narrowing of more than 50% of the luminal diameter is considered hemodynamically (and clinically) significant, although most lesions producing ischemia are associated with narrowing in excess of 70%. In those with strongly positive exercise ECGs or scintigraphic studies, three-vessel or left main disease may be present in 75–95% depending on the criteria used. **Intravascular ultrasound (IVUS)** is useful as an adjunct for assessing the results of angioplasty or stenting. In addition, IVUS is the invasive diagnostic method of choice for ostial left main lesions and coronary dissections. In **fractional flow reserve (FFR),** a pressure wire is used to measure the relative change in pressure across a coronary lesion after adenosine-induced hyperemia. Revascularization based on abnormal FFR improves clinical outcomes compared to revascularization of all angiographically stenotic lesions. FFR is an important invasive tool to aid with ischemia-driven revascularization and has become the standard tool to evaluate borderline lesions in cases in which the clinical team is evaluating the clinical and hemodynamic significance of a coronary stenosis. Additionally, pressures distally/pressures proximally during a wave-free period in diastole have been shown to demonstrate similar clinical outcomes to FFR, without the use of adenosine.

LV angiography is usually performed at the same time as coronary arteriography. Global and regional LV function are visualized, as well as mitral regurgitation if present. LV function is a major determinant of prognosis in CHD.

Differential Diagnosis

When atypical features are present—such as prolonged duration (hours or days) or darting, or knifelike pains at the apex or over the precordium—ischemia is less likely.

Anterior chest wall syndrome is characterized by a sharply localized tenderness of the intercostal muscles. Inflammation of the chondrocostal junctions may result in diffuse chest pain that is also reproduced by local pressure **(Tietze syndrome).** Intercostal neuritis (due to herpes zoster or diabetes mellitus, for example) also mimics angina.

Cervical or thoracic spine disease involving the dorsal roots produces sudden sharp, severe chest pain suggesting angina in location and "radiation" but related to specific movements of the neck or spine, recumbency, and straining or lifting. Pain due to cervical or thoracic disk disease involves the outer or dorsal aspect of the arm and the thumb and index fingers rather than the ring and little fingers.

Reflux esophagitis, peptic ulcer, chronic cholecystitis, esophageal spasm, and functional GI disease may produce pain suggestive of angina pectoris. The picture may be especially confusing because ischemic pain may also be associated with upper GI symptoms, and esophageal motility disorders may be improved by nitrates and calcium channel blockers. Assessment of esophageal motility may be helpful.

Degenerative and inflammatory lesions of the left shoulder and thoracic outlet syndromes may cause chest pain due to nerve irritation or muscular compression; the symptoms are usually precipitated by movement of the arm and shoulder and are associated with paresthesias.

Pneumonia, PE, and spontaneous pneumothorax may cause chest pain as well as dyspnea. Dissection of the thoracic aorta can cause severe chest pain that is commonly felt in the back; it is sudden in onset, reaches maximum intensity immediately, and may be associated with changes in pulses. Other cardiac disorders, such as mitral valve prolapse, HCM, myocarditis, pericarditis, aortic valve disease, or RVH, may cause atypical chest pain or even myocardial ischemia.

Treatment

Sublingual nitroglycerin is the medication of choice for acute management; it acts in about 1–2 minutes. As soon as the attack begins, one fresh tablet is placed under the tongue. This may be repeated at 3- to 5-minute intervals, but if pain is not relieved or improving after 5 minutes, the patient should call 9-1-1; pain not responding to three tablets or lasting more than 20 minutes may represent evolving infarction. The dosage (0.3, 0.4, or 0.6 mg) and the number of tablets to be used before seeking further medical attention must be individualized. Nitroglycerin buccal spray is also available as a metered (0.4 mg) delivery system. It has the advantage of being more convenient for

patients who have difficulty handling the pills and of being more stable.

Prevention of Further Attacks

A. Aggravating Factors

Angina may be aggravated by hypertension, LV failure, arrhythmia (usually tachycardias), strenuous activity, cold temperatures, and emotional states. These factors should be identified and treated when possible.

B. Nitroglycerin

Nitroglycerin, 0.3–0.6 mg sublingually or 0.4–0.8 mg translingually by spray, should be taken 5 minutes before any activity likely to precipitate angina. Sublingual isosorbide dinitrate (2.5–5 mg) is only slightly longer-acting than sublingual nitroglycerin.

C. Long-Acting Nitrates

Longer-acting nitrate preparations include isosorbide dinitrate, 10–40 mg orally three times daily; isosorbide mononitrate, 10–40 mg orally twice daily or 60–120 mg once daily in a sustained-release preparation; oral sustained-release nitroglycerin preparations, 6.25–12.5 mg two to four times daily; nitroglycerin ointment, 2% ointment, 0.5–2 inches (7.5–30 mg in the morning and 6 hours later); and transdermal nitroglycerin patches that deliver nitroglycerin at rates of 0.2, 0.4, and 0.6 mg/hour rate (0.1–0.8 mg/hour), and should be taken off after 12–14 hours of use for a 10–12 hour patch-free interval daily. The main limitation to long-term nitrate therapy is *tolerance*, which can be limited by using a regimen that includes a minimum 8- to 10-hour period per day without nitrates. Isosorbide dinitrate can be given three times daily, with the last dose after dinner, or longer-acting isosorbide mononitrate once daily. Transdermal nitrate preparations should be removed overnight in most patients.

Nitrate therapy is often limited by headache. Other side effects include nausea, light-headedness, and hypotension. Importantly, phosphodiesterase inhibitors used commonly for erectile dysfunction should not be taken within 24 hours of nitrate use.

D. Beta-Blockers

Beta-blockers are the only antianginal agents that have been demonstrated to prolong life in patients with coronary disease (post-MI). **Beta-blockers should be considered for first-line therapy in most patients with chronic angina** and are recommended as such by the stable ischemic heart disease guidelines (Figure 10–8).

Beta-blockers with intrinsic sympathomimetic activity, such as pindolol, are less desirable because they may exacerbate angina in some individuals and have not been effective in secondary prevention trials. The pharmacology and side effects of the beta-blockers are discussed in Chapter 11 (see Table 11–9). The dosages of all these medications when given for angina are similar. The major contraindications are severe bronchospastic disease, bradyarrhythmias, and decompensated heart failure.

E. Ranolazine

Ranolazine is indicated for chronic angina. Ranolazine has no effect on heart rate and BP, and it has been shown in clinical trials to prolong exercise duration and time to angina, both as monotherapy and when administered with conventional antianginal therapy. It is safe to use with erectile dysfunction medications. The usual dose is 500 mg orally twice a day. Because it can cause QT prolongation, it is contraindicated in patients with existing QT prolongation; in patients taking QT prolonging medications, such as class I or III antiarrhythmics (eg, quinidine, dofetilide, sotalol); and in those taking potent and moderate CYP450 3A inhibitors (eg, clarithromycin and rifampin). Of interest, in spite of the QT prolongation, there is a significantly lower rate of ventricular arrhythmias with its use following acute coronary syndromes, as shown in the MERLIN trial.

F. Calcium Channel Blocking Agents

Unlike the beta-blockers, calcium channel blockers have *not* been shown to reduce mortality postinfarction and in some cases have increased ischemia and mortality rates. This appears to be the case with some dihydropyridines (eg, nifedipine) and with diltiazem and verapamil in patients with clinical heart failure or moderate to severe LV dysfunction. Meta-analyses have suggested that short-acting nifedipine in moderate to high doses causes an *increase* in mortality. It is uncertain whether these findings are relevant to longer-acting dihydropyridines. Nevertheless, considering the uncertainties and the lack of demonstrated favorable effect on outcomes, calcium channel blockers should be considered third-line anti-ischemic medications in the postinfarction patient. Similarly, these agents, with the exception of amlodipine (which proved safe in patients with heart failure in the PRAISE-2 trial), should be avoided in patients with heart failure or low EFs.

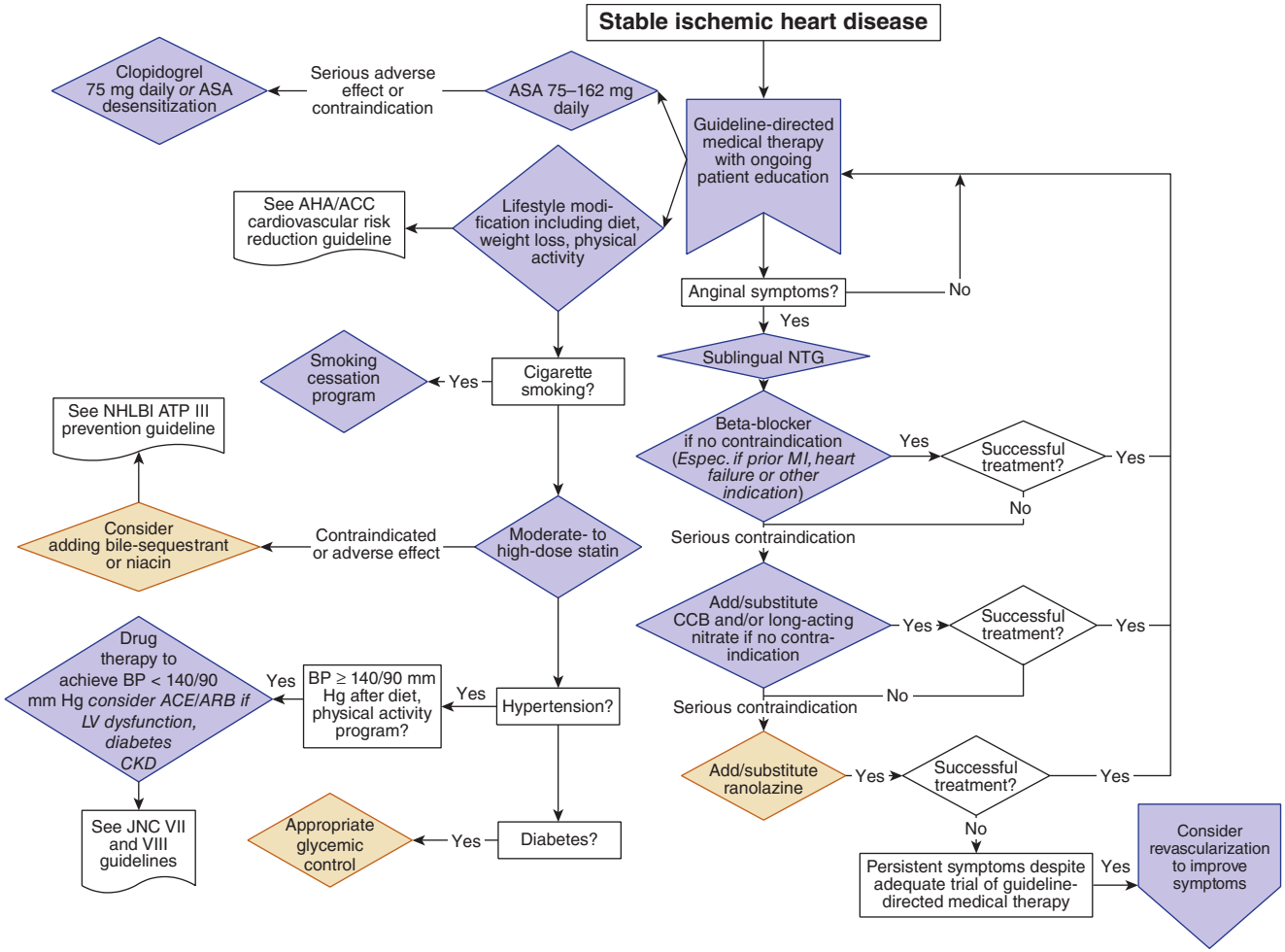
The pharmacologic effects and side effects of the calcium channel blockers are discussed in Chapter 11 and summarized in Table 11–7. Diltiazem, amlodipine, and verapamil are preferable because they produce less reflex tachycardia and because the former, at least, may cause fewer side effects. Nifedipine, nicardipine, and amlodipine are also approved agents for angina. Isradipine, felodipine, and nisoldipine are not approved for angina but probably are as effective as the other dihydropyridines.

G. Ivabradine

Ivabradine selectively blocks the I_f current and specifically lowers heart rate. It has been shown to reduce angina in patients with chronic stable angina and is approved in Europe. However, the SIGNIFY trial found no overall difference in clinical outcomes in patients without heart failure and angina and that there may have been harm for patients with significant angina with regard to outcomes of cardiovascular death and MI.

H. Alternative and Combination Therapies

Patients who do not respond to one class of antianginal medication often respond to another. It may, therefore, be



▲ **Figure 10–8.** Algorithm for guideline-directed medical therapy for patients with stable ischemic heart disease. The use of bile acid sequestrant is relatively contraindicated when triglycerides are 200 mg/dL or higher and contraindicated when triglycerides are 500 mg/dL or higher. Dietary supplement niacin must not be used as a substitute for prescription niacin. AHA/ACC, American Heart Association/American College of Cardiology; ASA, aspirin; BP, blood pressure; CCB, calcium channel blocker; NTG, nitroglycerin. (Reprinted with permission Circulation. 2012;126:e354–e471 ©2012 American Heart Association, Inc.)

worthwhile to use an alternative agent before progressing to combinations. **The stable ischemic heart disease guidelines recommend starting with a beta-blocker as initial therapy, followed by calcium channel blockers, long-acting nitrates, or ranolazine.** A few patients will have further response to a regimen including all four agents.

I. Platelet-Inhibiting Agents

Several studies have demonstrated the benefit of antiplatelet medications for patients with stable and unstable vascular disease. Therefore, **unless contraindicated, aspirin (81 mg orally daily) should be prescribed for all patients with angina.** A $P2Y_{12}$ inhibitor **clopidogrel,** 75 mg orally daily, reduces vascular events in patients with stable vascular disease (as an alternative to aspirin) and in patients with acute coronary syndromes (in addition to aspirin). Thus, it is also a good alternative in aspirin-intolerant patients. Clopidogrel in addition to aspirin did not reduce MI, stroke, or cardiovascular death in the CHARISMA trial of patients with CVD or multiple risk factors, with about a 50% increase in bleeding. However, it might be reasonable to use combination clopidogrel and aspirin for certain high-risk patients with established coronary disease, as tested in the Dual Antiplatelet Therapy (DAPT) trial. Specifically, **prolonged use of dual antiplatelet therapy with aspirin and clopidogrel may be beneficial in patients post–percutaneous stenting with drug-eluting stents who have a low bleeding risk.**

Ticagrelor, a $P2Y_{12}$ inhibitor, has been shown to reduce cardiovascular events in patients with acute coronary syndromes. Additionally, in patients with prior MI, long-term treatment with ticagrelor plus aspirin reduced cardiovascular events compared to aspirin alone. In patients with peripheral artery disease, ticagrelor monotherapy did not reduce cardiovascular events compared to clopidogrel.

Vorapaxar is an inhibitor of the protease-activated receptor-1. It was shown to reduce cardiovascular events for patients with stable atherosclerosis with a history of MI or peripheral artery disease in the TRA 2P trial. It is contraindicated for patients with a history of stroke or TIA due to increased risk of intracranial hemorrhage.

Rivaroxaban, a direct factor Xa inhibitor, when used at a dose of 2.5 mg twice daily in addition to low-dose aspirin, was found to reduce cardiovascular events including cardiovascular death, MI, or stroke when compared to aspirin monotherapy in patients with known CAD or peripheral artery disease. This agent is approved and provides another option for patients.

Current guidelines recommend **dual antiplatelet therapy (aspirin and $P2Y_{12}$ therapy) in patients with recent MI (within 1 year) or recent stenting (within 6 months) and for prolonged therapy (more than 1 year) in patients at high ischemic risk (multivessel coronary disease or polyvascular disease) and low bleeding risk.**

J. Risk Reduction

Patients with coronary disease should undergo aggressive **risk factor modification.** This approach, with a particular focus on statin treatment, treating hypertension, stopping smoking, and exercise and weight control (especially for patients with metabolic syndrome or at risk for diabetes), may markedly improve outcomes. For patients with diabetes and CVD, there is uncertainty about the optimal target blood sugar control. The ADVANCE trial suggested some benefit for tight blood sugar control with target HbA_{1C} of 6.5% or less, but the ACCORD trial found that routine aggressive targeting for blood sugar control to HbA_{1C} to less than 6.0% in patients with diabetes and coronary disease was associated with *increased* mortality. Therefore, tight blood sugar control should be avoided particularly in patients with a history of severe hypoglycemia, long-standing diabetes, and advanced vascular disease. Aggressive BP control (target systolic BP less than 120 mm Hg) in the ACCORD trial was *not* associated with reduction in CHD events despite reducing stroke. In contrast, the SPRINT trial, which did not include diabetic patients, demonstrated a reduction in cardiovascular events in patients with a reduction in death from any cause and reduction in MI with a goal systolic BP of less than 120 mm Hg versus of goal of less than 140 mm Hg. Some increase in adverse events was noted. Based on this and the totality of results, **the AHA has recommended defining hypertension at the 130 mm Hg level**.

K. Revascularization

1. Indications—There is general agreement that otherwise healthy patients in the following groups should undergo revascularization: (1) patients with unacceptable symptoms despite medical therapy to its tolerable limits; (2) patients with left main coronary artery stenosis greater than 50% with or without symptoms; (3) patients with three-vessel disease with LV dysfunction (EF less than 50% or previous transmural infarction); (4) patients with unstable angina who after symptom control by medical therapy continue to exhibit ischemia on exercise testing or monitoring; and (5) post-MI patients with continuing angina or severe ischemia on noninvasive testing. The use of revascularization for patients with acute coronary syndromes and acute ST-segment elevation MI (STEMI) is discussed below.

Data from the COURAGE trial have shown that for patients with chronic angina and disease suitable for PCI, PCI in addition to stringent guideline-directed medical therapy aimed at both risk reduction and anti-anginal care offers no mortality benefit beyond excellent medical therapy alone, and relatively moderate long-term symptomatic improvement. Therefore, **for patients with mild to moderate CAD and limited symptoms, revascularization may not provide significant functional status quality-of-life benefit.** For patients with moderate to significant coronary stenosis, such as those who have two-vessel disease associated with underlying LV dysfunction, anatomically critical lesions (greater than 90% proximal stenoses, especially of the proximal left anterior descending artery), or physiologic evidence of severe ischemia (early positive exercise tests, large exercise-induced thallium scintigraphic defects, or frequent episodes of ischemia on ambulatory monitoring), a heart team consisting of revascularization physicians (interventional cardiologists and surgeons) may be required to review and provide patients with the best revascularization options.

The ISCHEMIA trial found that for patients with moderate to severe ischemia on stress testing, coronary

angiography and revascularization did not reduce the risk of cardiovascular death, MI, hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. Thus, in the context of optimal medical therapy to prevent cardiovascular events, a higher threshold for whom to evaluate with stress tests and coronary angiography may be reasonable.

2. Type of procedure—

A. Percutaneous coronary intervention including stenting—PCI, including balloon angioplasty and coronary stenting, can effectively open stenotic coronary arteries. Coronary stenting, with either bare metal stents or drug-eluting stents, has substantially reduced restenosis. Stenting can also be used selectively for left main coronary stenosis, particularly when CABG is contraindicated or deemed high risk.

PCI is possible but often less successful in bypass graft stenoses. Experienced operators are able to successfully dilate more than 90% of lesions attempted. The major early complication is intimal dissection with vessel occlusion, although this is rare with coronary stenting. The use of intravenous platelet glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) substantially reduces the rate of periprocedural MI, and placement of intracoronary stents markedly improves initial and long-term angiographic results, especially with complex and long lesions. After percutaneous coronary intervention, all patients should have CK-MB and troponin measured. The definition of a periprocedural infarction has been debated, with many experts advocating for a clinical definition that incorporates different enzyme cutpoints, angiographic findings, and electrocardiographic evidence. Acute thrombosis after stent placement can largely be prevented by aggressive antithrombotic therapy (long-term aspirin, 81–325 mg, plus clopidogrel, 300–600 mg loading dose followed by 75 mg daily, for between 30 days and 1 year, and with acute use of platelet glycoprotein IIb/IIIa inhibitors).

A major limitation with PCI has been **restenosis,** which occurs in the first 6 months in less than 10% of vessels treated with drug-eluting stents, 15–30% of vessels treated with bare metal stents, and 30–40% of vessels without stenting. Factors associated with higher restenosis rates include diabetes, small luminal diameter, longer and more complex lesions, and lesions at coronary ostia or in the left anterior descending coronary artery. Drug-eluting stents that elute antiproliferative agents, such as sirolimus, everolimus, zotarolimus, or paclitaxel, have substantially reduced restenosis. In-stent restenosis is often treated with restenting with drug-eluting stents, and rarely with brachytherapy. The nearly 2 million PCIs performed worldwide per year far exceed the number of CABG operations, but the rationale for many of the procedures performed in patients with stable angina should be for angina symptom reduction. Moreover, data published in 2021 reported that 706,263 PCIs were performed in the United States from 2018 to 2019.

The COURAGE trial and the ORBITA sham-controlled trial have confirmed earlier studies in showing that, even for patients with moderate anginal symptoms and positive stress tests, PCI provides no benefit over medical therapy with respect to death or MI. PCI was more effective at relieving angina, although most patients in the medical group had improvement in symptoms. PCI was also not more effective than optimal medical therapy for exercise time in patients with one vessel coronary disease. Thus, **in patients with mild or moderate stable symptoms, aggressive lipid-lowering and antianginal therapy may be a preferable initial strategy, reserving PCI for patients with significant and refractory symptoms or for those who are unable to take the prescribed medicines.**

Several studies of PCI, including those with drug-eluting stents, versus CABG in patients with multivessel disease have been reported. The SYNTAX trial as well as previously performed trials with drug-eluting stent use in PCI patients show comparable mortality and infarction rates over follow-up periods of 1–3 years but a high rate (approximately 40%) of repeat procedures following PCI. Stroke rates are higher with CABG. As a result, the choice of revascularization procedure may depend on details of coronary anatomy and is often a matter of patient preference. However, it should be noted that less than 20% of patients with multivessel disease meet the entry criteria for the clinical trials, so these results cannot be generalized to all multivessel disease patients. Outcomes with percutaneous revascularization in patients with diabetes have generally been inferior to those with CABG. The FREEDOM trial demonstrated that **CABG surgery was superior to PCI with regard to death, MI, and stroke for patients with diabetes and multivessel coronary disease** at 5 years across all subgroups of SYNTAX score anatomy.

B. Coronary artery bypass grafting—CABG can be accomplished with a very low mortality rate (1–3%) in otherwise healthy patients with preserved cardiac function. However, the mortality rate of this procedure rises to 4–8% in older individuals and in patients who have had a prior CABG.

Grafts using one or both internal mammary arteries (usually to the left anterior descending artery or its branches) provide the best long-term results in terms of patency and flow. Segments of the saphenous vein (or, less optimally, other veins) or the radial artery interposed between the aorta and the coronary arteries distal to the obstructions are also used. One to five distal anastomoses are commonly performed.

Minimally invasive surgical techniques may involve a limited sternotomy, lateral thoracotomy (MIDCAB), or thoracoscopy (port-access). They are more technically demanding, usually not suitable for more than two grafts, and do not have established durability. Bypass surgery can be performed both on circulatory support (on-pump) and without direct circulatory support (off-pump). Randomized trial data have not shown a benefit with off-pump bypass surgery, but minimally invasive surgical techniques allow earlier postoperative mobilization and discharge.

The operative mortality rate is increased in patients with poor LV function (LVEF less than 35%) or those requiring additional procedures (valve replacement or ventricular aneurysmectomy). Patients over 70 years of age, patients undergoing repeat procedures, or those with important noncardiac disease (especially CKD and diabetes) or poor general health also have higher operative

mortality and morbidity rates, and full recovery is slow. Thus, CABG should be reserved for more severely symptomatic patients in this group. Early (1–6 months) graft patency rates average 85–90% (higher for internal mammary grafts), and subsequent graft closure rates are about 4% annually. Early graft failure is common in vessels with poor distal flow, while late closure is more frequent in patients who continue smoking and those with untreated hyperlipidemia. Antiplatelet therapy with aspirin improves graft patency rates. Smoking cessation and vigorous treatment of blood lipid abnormalities (particularly with statins) are necessary. Repeat revascularization may be necessary because of recurrent symptoms due to progressive native vessel disease and graft occlusions. Reoperation is technically demanding and less often fully successful than the initial operation. In addition, in patients with ischemic mitral regurgitation, mitral repair at the time of a CABG does not offer any clinical benefit.

L. Mechanical Extracorporeal Counterpulsation

Extracorporeal counterpulsation entails repetitive inflation of a high-pressure chamber surrounding the lower half of the body during the diastolic phase of the cardiac cycle for daily 1-hour sessions over a period of 7 weeks. Randomized trials have shown that extracorporeal counterpulsation reduces angina, thus it may be considered for relief of refractory angina in patients with stable coronary disease.

M. Neuromodulation

Spinal cord stimulation can be used to relieve chronic refractory angina. Spinal cord stimulators are subcutaneously implantable via a minimally invasive procedure under local anesthesia.

Prognosis

The prognosis of angina pectoris has improved with development of therapies aimed at secondary prevention. Mortality rates vary depending on the number of vessels diseased, the severity of obstruction, the status of LV function, and the presence of complex arrhythmias. Mortality rates are progressively higher in patients with one-, two-, and three-vessel disease and those with left main coronary artery obstruction (ranging from 1% per year to 25% per year). The outlook in individual patients is unpredictable, and nearly half of the deaths are sudden. Therefore, risk stratification is attempted. Patients with accelerating symptoms have a poorer outlook. Among stable patients, those whose exercise tolerance is severely limited by ischemia (less than 6 minutes on the Bruce treadmill protocol) and those with extensive ischemia by exercise ECG or scintigraphy have more severe anatomic disease and a poorer prognosis. The **Duke Treadmill Score,** based on a standard Bruce protocol exercise treadmill test, provides an estimate of risk of death at 1 year. The score uses time on the treadmill, amount of ST-segment depression, and presence of angina (Table 10–6).

Table 10–6. Duke Treadmill Score: calculation and interpretation.

Time in minutes on Bruce protocol		= _____
–5 × amount of depression (in mm)		= _____
–4 × angina index 0 = no angina on test 1 = angina, not limiting 2 = limiting angina		= _____
Total Summed Score	**Risk Group**	**Annual Mortality**
≥ 5	Low	0.25%
–10 to 4	Intermediate	1.25%
≤ –11	High	5.25%

When to Refer

All patients with new or worsening symptoms believed to represent progressive angina or a positive stress test for myocardial ischemia with continued angina despite medical therapy (or both) should be referred to a cardiologist.

When to Admit

- Patients with elevated cardiac biomarkers, ischemic ECG findings, or hemodynamic instability.
- Patients with new or worsened symptoms, possibly thought to be ischemic, but who lack high-risk features can be observed with serial ECGs and biomarkers and discharged if stress testing shows low-risk findings.

Castro-Dominguez YS et al. Predicting in-hospital mortality in patients undergoing percutaneous coronary intervention. J Am Coll Cardiol. 2021;78:216. [PMID: 33957239]

Knuuti J et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41:407. [PMID: 31504439]

Writing Committee Members; Gulati M et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021;78:e187. [PMID: 34756653]

CORONARY VASOSPASM & ANGINA OR MI WITH NORMAL CORONARY ARTERIOGRAMS

ESSENTIALS OF DIAGNOSIS

- Precordial chest pain, often occurring at rest during stress or without known precipitant, relieved rapidly by nitrates.
- ECG evidence of ischemia during pain, sometimes with ST-segment elevation.
- Angiographic demonstration of:
  - No significant obstruction of major coronary vessels.
  - Coronary spasm that responds to intracoronary nitroglycerin or calcium channel blockers.

General Considerations

Although most symptoms of myocardial ischemia result from fixed stenosis of the coronary arteries, intraplaque hemorrhage, or thrombosis at the site of lesions, some ischemic events may be precipitated or exacerbated by coronary vasoconstriction.

Spasm of the large coronary arteries with resulting decreased coronary blood flow may occur spontaneously or may be induced by exposure to cold, emotional stress, or vasoconstricting medications, such as ergot-derivative medications. Spasm may occur both in normal and in stenosed coronary arteries. Even MI may occur as a result of spasm in the absence of visible obstructive CHD, although most instances of such coronary spasm occur in the presence of coronary stenosis.

Cocaine can induce myocardial ischemia and infarction by causing coronary artery vasoconstriction or by increasing myocardial energy requirements. It also may contribute to accelerated atherosclerosis and thrombosis. The ischemia in **Prinzmetal (variant) angina** usually results from coronary vasoconstriction. It tends to involve the right coronary artery and there may be no fixed stenoses. Myocardial ischemia may also occur in patients with normal coronary arteries as a result of disease of the coronary microcirculation or abnormal vascular reactivity. MI without obstructive coronary disease is more frequent in women and has been shown to be due to atherosclerosis or ruptured plaques in 80% of cases. The 2020 ESC guidelines recommend cardiac MRI to aid in determining the cause of MI without obstructive coronary disease.

Clinical Findings

Ischemia may be silent or result in angina pectoris.

Prinzmetal (variant) angina is a clinical syndrome in which chest pain occurs without the usual precipitating factors and is associated with ST-segment elevation rather than depression. It often affects women under 50 years of age. It characteristically occurs in the early morning, awakening patients from sleep, and is apt to be associated with arrhythmias or conduction defects. It may be diagnosed by challenge with ergonovine (a vasoconstrictor), although the results of such provocation are not specific and it entails risk.

Treatment

Patients with chest pain associated with ST-segment elevation should undergo coronary arteriography to determine whether fixed stenotic lesions are present. If they are, aggressive medical therapy or revascularization is indicated, since the presence of these lesions may represent an unstable phase of the disease. If significant lesions are not seen, there may still be endothelial disruption and plaque rupture. If spasm is suspected, avoidance of precipitants, such as cigarette smoking and cocaine, is the top priority. Episodes of coronary spasm generally respond well to nitrates, and both nitrates and calcium channel blockers (including long-acting nifedipine, diltiazem, or amlodipine [see Table 11–7]) are effective prophylactically. By allowing unopposed alpha-1-mediated vasoconstriction, beta-blockers have exacerbated coronary vasospasm, but they may have a role in management of patients in whom spasm is associated with fixed stenoses.

When to Refer

All patients with persistent symptoms of chest pain that may represent spasm should be referred to a cardiologist.

ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

ESSENTIALS OF DIAGNOSIS

- Distinction in acute coronary syndrome between patients with and without ST-segment elevation at presentation is essential to determine need for reperfusion therapy.
- Fibrinolytic therapy is harmful in acute coronary syndrome without ST-segment elevation, unlike with ST-segment elevation, where acute reperfusion saves lives.
- Antiplatelet and anticoagulation therapies and coronary intervention are mainstays of treatment.

General Considerations

Acute coronary syndromes comprise the spectrum of unstable cardiac ischemia from unstable angina to acute MI. Acute coronary syndromes are classified based on the presenting ECG as either **ST-segment elevation MI (STEMI)** or **non–ST-segment elevation MI (NSTEMI)**. This allows for immediate classification and guides determination of whether patients should be considered for acute reperfusion therapy. The evolution of cardiac biomarkers then allows determination of whether MI has occurred.

Acute coronary syndromes represent a dynamic state in which patients frequently shift from one category to another, as new ST elevation can develop after presentation and cardiac biomarkers can become abnormal with recurrent ischemic episodes.

Clinical Findings

A. Symptoms and Signs

Patients with acute coronary syndromes generally have symptoms and signs of myocardial ischemia either at rest or with minimal exertion. These symptoms and signs are similar to the chronic angina symptoms described above, consisting of substernal chest pain or discomfort that may radiate to the jaw, left shoulder or arm. Dyspnea, nausea, diaphoresis, or syncope may either accompany the chest discomfort or may be the only symptom of acute coronary syndrome. *About one-third of patients with MI have no chest pain per se*—these patients tend to be older, female,

have diabetes, and be at higher risk for subsequent mortality. Patients with acute coronary syndromes have signs of heart failure in about 10% of cases, and this is also associated with higher risk of death.

Many hospitals have developed **chest pain observation units** to provide a systematic approach toward serial risk stratification to improve the triage process. In many cases, those who have not experienced new chest pain and have insignificant ECG changes and no cardiac biomarker elevation undergo treadmill exercise tests or imaging procedures to exclude ischemia at the end of an 8- to 24-hour period and are discharged directly from the emergency department if these tests are negative.

B. Laboratory Findings

Depending on the time from symptom onset to presentation, initial laboratory findings may be normal. The markers of cardiac myocyte necrosis (**myoglobin**, **CK-MB,** and **troponin I and T**) may all be used to identify acute MI, although *high-sensitivity troponin is now the recommended biomarker to diagnose acute MI* (see Laboratory Findings, Acute Myocardial Infarction with ST-Segment Elevation). In patients with STEMI, these initial markers are often within normal limits as the patient is being rushed to immediate reperfusion. In patients without ST-segment elevation, it is the presence of abnormal CK-MB or troponin values that are associated with myocyte necrosis and the diagnosis of MI. High-sensitivity troponin assays allow rapid assessment of MI in emergency departments by using 1- or 2-hour rule out algorithms. The universal definition of MI is a rise of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia, ECG changes of new ischemia, new Q waves, or imaging evidence of new loss of viable myocardium or new wall motion abnormality.

Serum creatinine is an important determinant of risk, and estimated creatinine clearance is important to guide dosing of certain antithrombotics, including eptifibatide and enoxaparin.

C. ECG

Many patients with acute coronary syndromes will exhibit ECG changes during pain—either ST-segment elevation, ST-segment depression, or T-wave flattening or inversion. Dynamic ST-segment shift is the most specific for acute coronary syndrome. ST-segment elevation in lead AVR suggests left main or three-vessel disease.

Treatment

A. General Measures

Treatment of acute coronary syndromes without ST elevation should be multifaceted. Patients who are at medium or high risk should be hospitalized, maintained at bed rest or at very limited activity for the first 24 hours, monitored, and given supplemental oxygen. Sedation with a benzodiazepine agent may help if anxiety is present.

B. Specific Measures

Figure 10–9 provides an algorithm for initial management of NSTEMI.

C. Antiplatelet and Anticoagulation Therapy

Patients should receive a combination of antiplatelet and anticoagulant agents on presentation. Fibrinolytic therapy should be *avoided* in patients without ST-segment elevation since they generally do not have an acute coronary occlusion, and the risk of such therapy appears to outweigh the benefit.

1. Antiplatelet therapy—

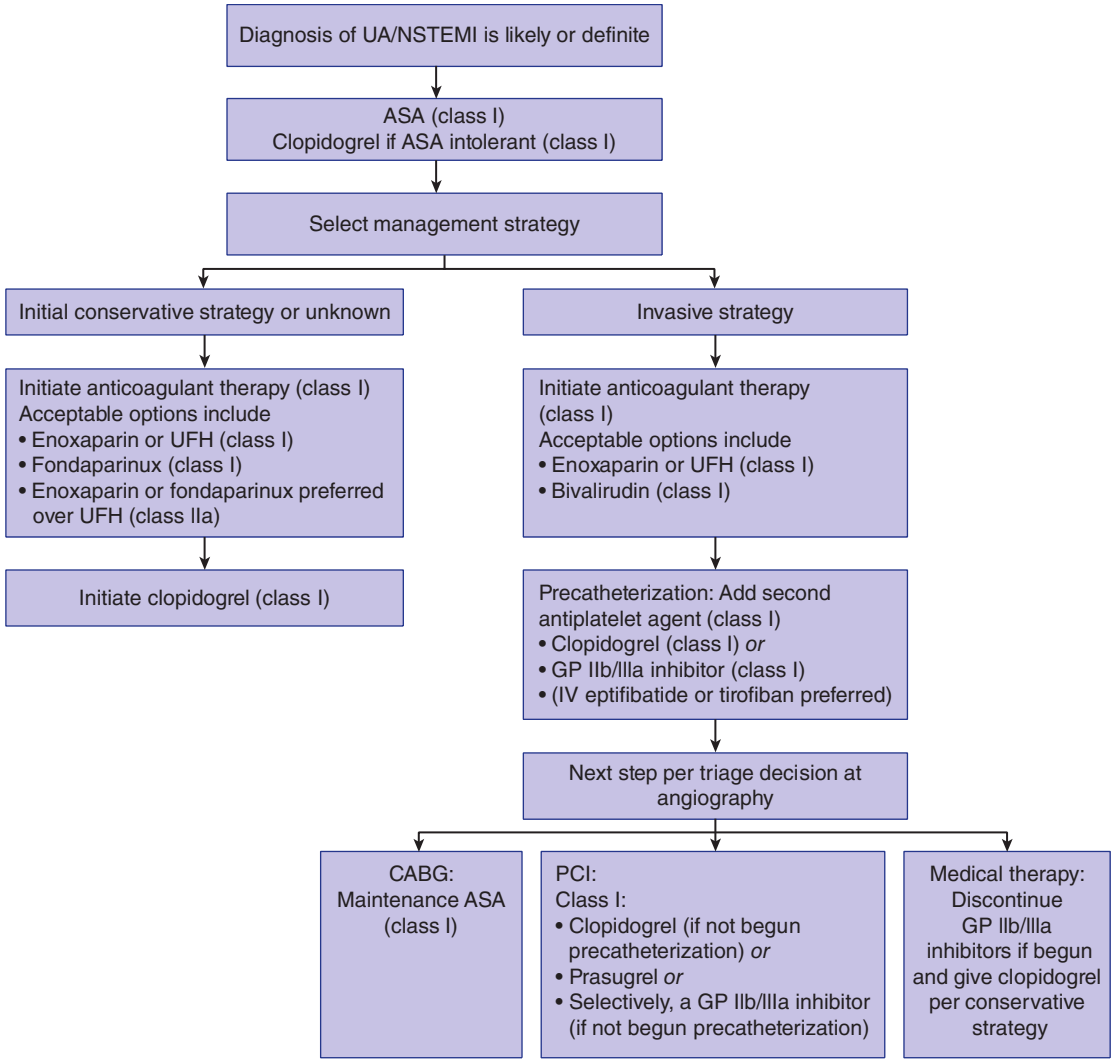
A. Aspirin—Aspirin, 162–325 mg loading dose, then 81 mg daily, should be commenced immediately and continued for the first month. The 2020 ESC guidelines for longer-term aspirin treatment recommend aspirin 75–100 mg/day as preferable to higher doses with or without coronary stenting.

B. P2Y12 inhibitors—ACC/AHA guidelines call for either a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel [at the time of PCI], or ticagrelor) as a class I recommendation. The ESC guidelines provide a stronger recommendation for a $P2Y_{12}$ inhibitor up-front, as a class IA recommendation for all patients. Both sets of guidelines recommend postponing elective CABG surgery for at least 5 days after the last dose of clopidogrel or ticagrelor and at least 7 days after the last dose of prasugrel, due to risk of bleeding.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial demonstrated a 20% reduction in the composite end point of cardiovascular death, MI, and stroke with the addition of clopidogrel (300-mg loading dose, 75 mg/day for 9–12 months) to aspirin in patients with non–ST-segment elevation acute coronary syndromes. The large CURRENT trial showed that "double-dose" clopidogrel (600-mg initial oral loading dose, followed by 150 mg orally daily) for 7 days reduced stent thrombosis with a modest increase in major (but not fatal) bleeding and, therefore, it is an option for patients with acute coronary syndrome undergoing PCI.

The ESC guidelines recommend ticagrelor for all patients at moderate to high risk for acute coronary syndrome (class I recommendation). Prasugrel is recommended for patients who have not yet received another $P2Y_{12}$ inhibitor, for whom a PCI is planned, and who are not at high risk for life-threatening bleeding. Clopidogrel is reserved for patients who cannot receive either ticagrelor or prasugrel. Some studies have shown an association between assays of residual platelet function and thrombotic risk during $P2Y_{12}$ inhibitor therapy, and both the European and the US guidelines do not recommend routine platelet function testing to guide therapy (class IIb recommendation).

Prasugrel is both more potent and has a faster onset of action than clopidogrel. The TRITON trial compared prasugrel with clopidogrel in patients with STEMI or NSTEMI in whom PCI was planned; prasugrel resulted in a 19% relative reduction in death from cardiovascular causes, MI,



▲ **Figure 10–9.** Flowchart for class I and class IIa recommendations for initial management of unstable angina/non–ST-segment elevation myocardial infarction (UA/NSTEMI). ASA, aspirin; CABG, coronary artery bypass grafting; GP IIb/IIIa, glycoprotein IIb/IIIa; LOE, level of evidence; UFH, unfractionated heparin. (Reprinted with permission Circulation. 2011;123:2022–2060 ©2011 American Heart Association, Inc.)

or stroke, at the expense of an increase in serious bleeding (including fatal bleeding). Stent thrombosis was reduced by half. Because patients with prior stroke or TIA had higher risk of intracranial hemorrhage, prasugrel is contraindicated in such patients. Bleeding was also higher in patients with low body weight (less than 60 kg) and age 75 years or older, and caution should be used in these populations. For patients with STEMI treated with PCI, prasugrel appears to be especially effective (compared to clopidogrel) without a substantial increase in bleeding. For patients who will not receive revascularization, prasugrel, when compared to clopidogrel, had no overall benefit in the TRILOGY trial (the dose of prasugrel was lowered for older adults). Prasugrel appears to be at least comparable to ticagrelor for patients with STEMI regarding safety and efficacy based on the ISAR-REACT 5 trial.

Ticagrelor has a faster onset of action than clopidogrel and a more consistent and potent effect. The PLATO trial showed that when ticagrelor was started at the time of presentation in acute coronary syndrome patients (UA/NSTEMI and STEMI), it reduced cardiovascular death, MI, and stroke by 16% when compared with clopidogrel. In addition, there was a 22% relative risk reduction in mortality with ticagrelor. The overall rates of bleeding were similar between ticagrelor and clopidogrel, although non–CABG-related bleeding was modestly higher.

The finding of a lesser treatment effect in the United States may have been related to use of higher-dose aspirin, and thus when using ticagrelor, low-dose aspirin (81 mg/day) is recommended.

c. Glycoprotein IIb/IIIa inhibitors—Small-molecule inhibitors of the platelet glycoprotein IIb/IIIa receptor are useful adjuncts in high-risk patients (usually defined by fluctuating ST-segment depression or positive biomarkers) with acute coronary syndromes, particularly when they are undergoing PCI. Tirofiban, 25 mcg/kg over 3 minutes, followed by 0.15 mcg/kg/minute, and eptifibatide, 180 mcg/kg bolus followed by a continuous infusion of 2 mcg/kg/minute, have both been shown to be effective. Downward dose adjustments of the infusions are required in patients with reduced kidney function. The bolus or loading dose remains unadjusted. For example, if the estimated creatinine clearance is below 50 mL/minute, the eptifibatide infusion should be cut in half to 1 mcg/kg/minute.

2. Anticoagulant therapy—

a. Heparin—Several trials have shown that LMWH (enoxaparin 1 mg/kg subcutaneously every 12 hours) is somewhat more effective than unfractionated heparin in preventing recurrent ischemic events in the setting of acute coronary syndromes. However, the SYNERGY trial showed that unfractionated heparin and enoxaparin had similar rates of death or (re)infarction in the setting of frequent early coronary intervention.

b. Fondaparinux—Fondaparinux, a specific factor Xa inhibitor given in a dose of 2.5 mg subcutaneously once a day, was found in the OASIS-5 trial to be equally effective as enoxaparin among 20,000 patients at preventing early death, MI, and refractory ischemia, and resulted in a 50% reduction in major bleeding. This reduction in major bleeding translated into a significant reduction in mortality (and in death or MI) at 30 days. While catheter-related thrombosis was more common during coronary intervention procedures with fondaparinux, the FUTURA trial found that it can be controlled by adding unfractionated heparin (in a dose of 85 units/kg without glycoprotein IIb/IIIa inhibitors, and 60 units/kg with glycoprotein IIb/IIIa inhibitors) during the procedure. Guidelines recommend fondaparinux, describing it as especially favorable for patients who are initially treated medically and who are at high risk for bleeding, such as elderly individuals.

c. Direct thrombin inhibitors—The ACUITY trial showed that bivalirudin appears to be a reasonable alternative to heparin (unfractionated heparin or enoxaparin) plus a glycoprotein IIb/IIIa antagonist for many patients with acute coronary syndromes who are undergoing early coronary intervention. Bivalirudin (without routine glycoprotein IIb/IIIa inhibitor) is associated with substantially less bleeding than heparin plus glycoprotein IIb/IIIa inhibitor, although it may have numerically increased cardiovascular events. The ISAR REACT-4 trial showed that bivalirudin has similar efficacy compared to abciximab but better bleeding outcomes in NSTEMI patients. Bivalrudin does not currently have an FDA-approved indication for NSTEMI care.

D. Temporary Discontinuation of Antiplatelet Therapy for Procedures

Patients who have had recent coronary stents are at risk for thrombotic events, including stent thrombosis, if $P2Y_{12}$ inhibitors are discontinued for procedures (eg, dental procedures or colonoscopy). If possible, these procedures should be delayed until the end of the necessary treatment period with $P2Y_{12}$ inhibitors, which generally is at least 1 month with bare metal stents and 3–6 months with drug-eluting stents. With newer generation drug-eluting stents, elective stenting patients with bleeding risk may have $P2Y_{12}$ inhibitors stopped before 3 months. Before that time, if a procedure is necessary, risk and benefit of continuing the antiplatelet therapy through the time of the procedure should be assessed. Aspirin should generally be continued throughout the period of the procedure. Patients with polymer-free drug coated stents who are at high risk for bleeding and receiving a short course of dual antiplatelet therapy had fewer cardiovascular and bleeding events. Likewise, in the MASTER-DAPT trial, patients at high risk for bleeding treated for 1 month with DAPT had noninferior outcomes with respect to major adverse cardiac events compared with longer duration DAPT with lower rates of bleeding. A cardiologist should be consulted before temporary discontinuation of these agents.

E. Nitroglycerin

Nitrates are first-line therapy for patients with acute coronary syndromes presenting with chest pain. Nonparenteral therapy with sublingual or oral agents or nitroglycerin ointment is usually sufficient. If pain persists or recurs, intravenous nitroglycerin should be started. The usual initial dosage is 10 mcg/minute. The dosage should be titrated upward by 10–20 mcg/minute (to a maximum of 200 mcg/minute) until angina disappears or mean arterial pressure drops by 10%. Careful—usually continuous—BP monitoring is required when intravenous nitroglycerin is used. Avoid hypotension (systolic BP less than 100 mm Hg). Tolerance to continuous nitrate infusion is common.

F. Beta-Blockers

Beta-blockers are an important part of the initial treatment of unstable angina unless otherwise contraindicated. The pharmacology of these agents is discussed in Chapter 11 and summarized in Table 11–9. Use of agents with intrinsic sympathomimetic activity should be avoided in this setting. Oral medication is adequate in most patients, but intravenous treatment with metoprolol, given as three 5-mg doses 5 minutes apart as tolerated and in the absence of heart failure, achieves a more rapid effect. Oral therapy should be titrated upward as BP permits.

G. Calcium Channel Blockers

Calcium channel blockers have *not* been shown to favorably affect outcome in unstable angina, and they should be used primarily as third-line therapy in patients with continuing angina who are taking nitrates and beta-blockers or those who are not candidates for these medications. In the

presence of nitrates and without accompanying beta-blockers, diltiazem or verapamil is preferred, since nifedipine and the other dihydropyridines are more likely to cause reflex tachycardia or hypotension. The initial dosage should be low, but upward titration should proceed steadily (see Table 11–7).

H. Statins

The PROVE-IT trial provides evidence for starting a statin in the days immediately following an acute coronary syndrome. In this trial, more intensive therapy with atorvastatin 80 mg/day, regardless of total or LDL cholesterol level, improved outcome compared to pravastatin 40 mg/day, with the curves of death or major cardiovascular event separating as early as 3 months after starting therapy. **High-intensity statins are recommended for all patients with acute coronary syndromes** (see Table 10–5).

Indications for Coronary Angiography

For patients with acute coronary syndrome, including NSTEMI, risk *stratification* is important for determining intensity of care. Several therapies, including glycoprotein IIb/IIIa inhibitors, LMWH heparin, and early invasive catheterization, have been shown to have the greatest benefit in higher-risk patients with acute coronary syndrome. As outlined in the ACC/AHA guidelines, patients with any high-risk feature (Table 10–7) generally warrant an early invasive strategy with catheterization and revascularization. For patients without these high-risk features, either an invasive or noninvasive approach, using exercise (or pharmacologic stress for patients unable to exercise) stress testing to identify patients who have residual ischemia and/or high risk, can be used. Moreover, based on the ICTUS trial, a strategy based on selective coronary angiography and revascularization for instability or inducible ischemia, or both, even for patients with positive troponin, is acceptable (ACC/AHA class IIb recommendation).

Two risk-stratification tools are available that can be used at the bedside, the **GRACE Risk Score** (http://www.outcomes-umassmed.org/grace) and the **TIMI Risk Score** (http://www.timi.org). The GRACE Risk Score, which applies to patients with or without ST elevation, was developed in a more generalizable registry population and has better discrimination of risk. It includes age (as a continuous variable), Killip class, BP, ST-segment deviation, cardiac arrest at presentation, serum creatinine, elevated creatine kinase (CK)-MB or troponin, and heart rate. The TIMI Risk Score includes seven variables: age 65 years or older, three or more cardiac risk factors, prior coronary stenosis of 50% or more, ST-segment deviation, two anginal events in prior 24 hours, aspirin in prior 7 days, and elevated cardiac markers.

When to Refer

- All patients with acute MI should be referred to a cardiologist.
- Patients who are taking a $P2Y_{12}$ inhibitor following coronary stenting should consult a cardiologist before discontinuing treatment for nonemergency procedures.

Table 10–7. Indications for catheterization and percutaneous coronary intervention.[1]

Acute coronary syndromes (unstable angina and non-ST elevation MI)	
Class I	Early invasive strategy for any of the following high-risk indicators:
	Recurrent angina/ischemia at rest or with low-level activity
	Elevated troponin
	ST-segment depression
	Recurrent ischemia with evidence of HF
	High-risk stress test result
	EF < 40%
	Hemodynamic instability
	Sustained ventricular tachycardia
	PCI within 6 months
	Prior CABG
	In the absence of these findings, either an early conservative or early invasive strategy
Class IIa	Early invasive strategy for patients with repeated presentations for ACS despite therapy
Class III	Extensive comorbidities in patients in whom benefits of revascularization are not likely to outweigh the risks
	Acute chest pain with low likelihood of ACS
Acute MI after fibrinolytic therapy	
Class I	Cardiogenic shock or acute severe heart failure that develops after initial presentation
	Intermediate- or high-risk findings on predischarge noninvasive ischemia testing
	Spontaneous or easily provoked myocardial ischemia
Class IIa	Failed reperfusion or reocclusion after fibrinolytic therapy
	Stable[2] patients after successful fibrinolysis, before discharge and ideally between 3 and 24 hours

[1]Class I indicates treatment is useful and effective, IIa indicates weight of evidence is in favor of usefulness/efficacy, class IIb indicates weight of evidence is less well established, and class III indicates intervention is not useful/effective and may be harmful. Level of evidence A recommendations are derived from large-scale randomized trials, and B recommendations are derived from smaller randomized trials or carefully conducted observational analyses.

[2]Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; HF, heart failure; PCI, percutaneous coronary intervention.

Data from O'Gara PT et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127: e362–e425.

Collet JP et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42:1289. [PMID: 32860058]
Valgimigli M et al; MASTER DAPT Investigators. Dual antiplatelet therapy after PCI in patients at high bleeding risk. N Engl J Med. 2021;385:1643. [PMID: 34449185]

ACUTE MI WITH ST-SEGMENT ELEVATION

ESSENTIALS OF DIAGNOSIS

- Sudden but not instantaneous development of prolonged (> 30 minutes) anterior chest discomfort (sometimes felt as "gas" or pressure).
- Sometimes painless, masquerading as acute heart failure, syncope, stroke, or shock.
- ECG: ST-segment elevation or left bundle branch block.
- Immediate reperfusion treatment is warranted.
- Primary PCI within 90 minutes of first medical contact is the goal and is superior to fibrinolytic therapy.
- Fibrinolytic therapy within 30 minutes of hospital presentation is the goal and reduces mortality if given within 12 hours of onset of symptoms.

General Considerations

STEMI results, in most cases, from an occlusive coronary thrombus at the site of a preexisting (though not necessarily severe) atherosclerotic plaque. More rarely, infarction may result from prolonged vasospasm, inadequate myocardial blood flow (eg, hypotension), or excessive metabolic demand. Very rarely, MI may be caused by embolic occlusion, vasculitis, aortic root or coronary artery dissection, or aortitis. Cocaine, a cause of infarction, should be considered in young individuals without risk factors. A condition that may mimic STEMI is stress cardiomyopathy (also referred to as **tako-tsubo** or **apical ballooning syndrome**). ST elevation connotes an acute coronary occlusion and warrants *immediate* reperfusion therapy with activation of emergency services.

Clinical Findings

A. Symptoms

1. Premonitory pain—There is usually a worsening in the pattern of angina preceding the onset of symptoms of MI; classically the onset of angina occurs with minimal exertion or at rest.

2. Pain of infarction—Unlike anginal episodes, most infarctions occur *at rest*, and more commonly in the early morning. The pain is similar to angina in location and radiation but it may be more severe, and it builds up rapidly or in waves to maximum intensity over a few minutes or longer. Nitroglycerin has little effect; even opioids may not relieve the pain.

3. Associated symptoms—Patients may break out in a cold sweat, feel weak and apprehensive, and move about, seeking a position of comfort. They prefer not to lie quietly. Light-headedness, syncope, dyspnea, orthopnea, cough, wheezing, nausea and vomiting, or abdominal bloating may be present singly or in any combination.

4. Painless infarction—One-third of patients with acute MI present *without* chest pain, and these patients tend to be undertreated and have poor outcomes. Older patients, women, and patients with diabetes mellitus are more likely to present without chest pain. As many as 25% of infarctions are detected on routine ECG without any recallable acute episode.

5. Sudden death and early arrhythmias—Of all deaths from MI, about half occur before the patients arrive at the hospital, with death presumably caused by ventricular fibrillation.

B. Signs

1. General—Patients may appear anxious and sometimes are sweating profusely. The heart rate may range from marked bradycardia (most commonly in inferior infarction) to tachycardia, low cardiac output, or arrhythmia. The BP may be high, especially in former hypertensive patients, or low in patients with shock. Respiratory distress usually indicates heart failure. Fever, usually low grade, may appear after 12 hours and persist for several days.

2. Chest—The **Killip classification** is the standard way to classify heart failure in patients with acute MI and has powerful prognostic value. Killip class I is absence of rales and S_3, class II is rales that do not clear with coughing over one-third or less of the lung fields or presence of an S_3, class III is rales that do not clear with coughing over more than one-third of the lung fields, and class IV is cardiogenic shock (rales, hypotension, and signs of hypoperfusion).

3. Heart—The cardiac examination may be unimpressive or very abnormal. Jugular venous distention reflects RA hypertension, and a Kussmaul sign (failure of decrease of jugular venous pressure with inspiration) is suggestive of RV infarction. Soft heart sounds may indicate LV dysfunction. Atrial gallops (S_4) are the rule, whereas ventricular gallops (S_3) are less common and indicate significant LV dysfunction. Mitral regurgitation murmurs are not uncommon and may indicate papillary muscle dysfunction or, rarely, rupture. Pericardial friction rubs are uncommon in the first 24 hours but may appear later.

4. Extremities—Edema is usually not present. Cyanosis and cold temperature indicate low output. The peripheral pulses should be noted, since later shock or emboli may alter the examination.

C. Laboratory Findings

Cardiac-specific markers of myocardial damage include quantitative determinations of CK-MB, highly sensitive

and conventional troponin I, and troponin T. Each of these tests may become positive as early as 4–6 hours after the onset of an MI and should be abnormal by 8–12 hours. Troponins are more sensitive and specific than CK-MB. "Highly sensitive" or "fourth-generation" troponin assays were approved in 2017. They are the standard assays in most of Europe, with a 10- to 100-fold lower limit of detection, allowing MI to be detected earlier, using the change in value over 3 hours.

Circulating levels of troponins may remain elevated for 5–7 days or longer and therefore are generally not useful for evaluating suspected early reinfarction. Elevated CK-MB generally normalizes within 24 hours, thus being more helpful for evaluation of reinfarction. Low-level elevations of troponin in patients with severe CKD may not be related to acute coronary disease but rather a function of the physiologic washout of the marker. While many conditions including chronic heart failure are associated with elevated levels of the high-sensitivity troponin assays, these assays may be especially useful when negative to exclude MI in patients reporting chest pain.

D. ECG

The extent of the ECG abnormalities, especially the sum of the total amount of ST-segment deviation, is a good indicator of the extent of acute infarction and risk of subsequent adverse events. The classic evolution of changes is from peaked ("hyperacute") T waves, to ST-segment elevation, to Q wave development, to T wave inversion. This may occur over a few hours to several days. The evolution of new Q waves (longer than 30 msec in duration and 25% of the R wave amplitude) is diagnostic, but Q waves do not occur in 30–50% of acute infarctions (**non-Q wave infarctions**). Left bundle branch block, especially when new (or not known to be old), in a patient with symptoms of an acute MI is considered to be a **"STEMI equivalent"**; reperfusion therapy is indicated for the affected patient. Concordant ST elevation (ie, ST elevation in leads with an overall positive QRS complex) with left bundle branch block is a specific finding indicating STEMI.

E. Chest Radiography

The chest radiograph may demonstrate signs of heart failure, but these changes often lag behind the clinical findings. Signs of aortic dissection, including mediastinal widening, should be sought as a possible alternative diagnosis.

F. Echocardiography

Echocardiography provides convenient *bedside assessment* of LV global and regional function. This can help with the diagnosis and management of infarction; echocardiography has been used successfully to make judgments about admission and management of patients with suspected infarction, including in patients with ST-segment elevation or left bundle branch block of uncertain significance, since normal wall motion makes an infarction unlikely. Doppler echocardiography is generally the most convenient procedure for diagnosing postinfarction mitral regurgitation or VSD.

G. Other Noninvasive Studies

Diagnosis of MI and extent of MI can be assessed by various imaging studies in addition to echocardiography. **MRI with gadolinium contrast enhancement** is the most sensitive test to detect and quantitate extent of infarction, with the ability to detect as little as 2 g of MI. **Technetium-99m pyrophosphate scintigraphy,** when injected at least 18 hours postinfarction, complexes with calcium in necrotic myocardium to provide a "hot spot" image of the infarction. This test is insensitive to small infarctions, and false-positive studies occur, so its use is limited to patients in whom the diagnosis by ECG and enzymes is not possible—principally those who present several days after the event or have intraoperative infarctions. **Scintigraphy with thallium-201** or **technetium-based perfusion tracers** will demonstrate "cold spots" in regions of diminished perfusion, which usually represent infarction when the radiotracer is administered at rest, but abnormalities do not distinguish recent from old damage. All of these tests may be considered after the patient has had revascularization.

H. Hemodynamic Measurements

These can be helpful in managing the patient with suspected cardiogenic shock. Use of PA catheters, however, has generally not been associated with better outcomes and should be limited to patients with severe hemodynamic compromise for whom the information would be anticipated to change management.

Treatment

A. Aspirin, $P2Y_{12}$ Inhibitors (Prasugrel, Ticagrelor, and Clopidogrel)

All patients with definite or suspected acute MI should receive aspirin at a dose of 162 mg or 325 mg at once regardless of whether fibrinolytic therapy is being considered or the patient has been taking aspirin. Chewable aspirin provides more rapid blood levels. Patients with a definite aspirin allergy should be treated with a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor).

$P2Y_{12}$ inhibitors, in combination with aspirin, have been shown to provide important benefits in patients with acute STEMI. Thus, guidelines call for a **$P2Y_{12}$ inhibitor to be added to aspirin for all patients with STEMI, regardless of whether reperfusion is given, and continued for at least 14 days, and generally for 1 year.** The preferred $P2Y_{12}$ inhibitors are prasugrel (60 mg orally on day 1, then 10 mg daily) or ticagrelor (180 mg orally on day 1, then 90 mg twice daily). Both of these medications demonstrated superior outcomes to clopidogrel in clinical studies of primary PCI. Clopidogrel should be administered as a loading dose of 300–600 mg orally for faster onset of action than the 75 mg maintenance dose. With fibrinolytic therapy, ticagrelor appears to be a reasonable alternative to clopidogrel, at least after an initial clopidogrel dose. Prasugrel is contraindicated in patients with a history of stroke or who are older than 75 years.

B. Reperfusion Therapy

Patients with STEMI who seek medical attention within 12 hours of the onset of symptoms should be treated with reperfusion therapy, either primary PCI or fibrinolytic therapy. Patients without ST-segment elevation (previously labeled "non-Q wave" infarctions) do not benefit, and may derive harm, from thrombolysis.

1. Primary percutaneous coronary intervention—Immediate coronary angiography and primary PCI (including stenting) of the infarct-related artery have been shown to be *superior* to thrombolysis when done by experienced operators in high-volume centers with rapid time from first medical contact to intervention ("door-to-balloon"). US and European guidelines call for first medical contact or door-to-balloon times of 90 minutes or less. Several trials have shown that if efficient transfer systems are in place, transfer of patients with acute MI from hospitals without primary PCI capability to hospitals with primary PCI capability with first door-to-device times of 120 minutes or less can improve outcome compared with fibrinolytic therapy at the presenting hospital, although this requires sophisticated systems to ensure rapid identification, transfer, and expertise in PCI. Because PCI also carries a lower risk of hemorrhagic complications, including intracranial hemorrhage, it may be the preferred strategy in many older patients and others with contraindications to fibrinolytic therapy (see Table 10–8 for factors to consider in choosing fibrinolytic therapy or primary PCI).

A. Stenting—PCI with stenting is standard for patients with acute MI. Although randomized trials have shown a benefit with regard to fewer repeat interventions for restenosis with the use of drug-eluting stents in STEMI patients, and current generation drug-eluting stents have similar or lower rates of stent thrombosis than bare metal stents, bare metal stents may still be used for selected patients without the ability to obtain and comply with $P2Y_{12}$ inhibitor therapy. In the subgroup of patients with cardiogenic shock, early catheterization and percutaneous or surgical revascularization are the preferred management and have been shown to reduce mortality.

"Facilitated" PCI, whereby a combination of medications (full- or reduced-dose fibrinolytic agents, with or without glycoprotein IIb/IIIa inhibitors) is given followed by immediate PCI, is *not* recommended. *Patients should be treated either with primary PCI or with fibrinolytic agents (and immediate rescue PCI for reperfusion failure), if it can be done promptly as outlined in the ACC/AHA and European guidelines.* Timely access to most appropriate reperfusion, including primary PCI, can be expanded with development of regional systems of care, including emergency medical systems and networks of hospitals. Patients treated with fibrinolytic therapy appear to have improved outcomes if transferred for routine coronary angiography and PCI within 24 hours. The AHA has a program called "Mission: Lifeline" to support the development of regional systems of care (http://www.heart.org/missionlifeline).

B. Antiplatelet therapy after drug-eluting or bare metal stents—In patients with an acute coronary syndrome, **dual antiplatelet therapy** is indicated for 1 year in all patients (including those with medical therapy and those patients undergoing revascularization irrespective of stent type). For patients undergoing elective or stable PCI, the duration of dual antiplatelet therapy is recommended for at least 1 month for patients receiving bare metal stents. For patients receiving drug-eluting stents for acute coronary syndromes, dual antiplatelet therapy is recommended for at least 1 year by the ACC/AHA and European guidelines. These recommendations are based both on the durations of therapies during the studies evaluating the stents, and the pathophysiologic understanding of the timing of endothelialization following bare metal versus drug-eluting stent implantation. The DAPT (Dual Antiplatelet Therapy) study showed fewer death, MI, and stroke events with longer (up to 30 months) dual antiplatelet therapy for patients who had received drug-eluting stents, but it also showed more bleeding and a tendency for higher mortality. Treatment with clopidogrel for longer than 1 year after drug-eluting stents, therefore, should be individualized based on thrombotic and bleeding risks.

2. Fibrinolytic therapy—

A. Benefit—Fibrinolytic therapy reduces mortality and limits infarct size in patients with STEMI (defined as 0.1 mV or more in two inferior or lateral leads or two contiguous precordial leads), or with left bundle branch block (not known to be old). The greatest benefit occurs if treatment is initiated within the first 3 hours after the onset of presentation, when up to a 50% reduction in mortality rate can be achieved. The magnitude of benefit declines rapidly thereafter, but a 10% relative mortality reduction can be achieved up to 12 hours after the onset of chest pain. The survival benefit is greatest in patients with large—usually anterior—infarctions. Primary PCI (including stenting) of the infarct-related artery, however, is superior to thrombolysis when done by experienced operators with rapid time from first medical contact to intervention ("door-to-balloon").

B. Contraindications—Major bleeding complications occur in 0.5–5% of patients, the most serious of which is intracranial hemorrhage. The major risk factors for intracranial bleeding are age 75 years or older, hypertension at presentation (especially over 180/110 mm Hg), low body weight (less than 70 kg), and the use of fibrin-specific fibrinolytic agents (alteplase, reteplase, tenecteplase). Although patients over age 75 years have a much higher mortality rate with acute MI and therefore may derive greater benefit, the risk of severe bleeding is also higher, particularly among patients with risk factors for intracranial hemorrhage, such as severe hypertension or recent stroke. Patients presenting more than 12 hours after the onset of chest pain may also derive a small benefit, particularly if pain and ST-segment elevation persist, but rarely does this benefit outweigh the attendant risk.

Absolute contraindications to fibrinolytic therapy include previous hemorrhagic stroke, other strokes or cerebrovascular events within 1 year, known intracranial neoplasm, recent head trauma (including minor trauma), active internal bleeding (excluding menstruation), or suspected aortic dissection. Relative contraindications are BP

greater than 180/110 mm Hg at presentation, other intracerebral pathology not listed above as a contraindication, known bleeding diathesis, trauma within 2–4 weeks, major surgery within 3 weeks, prolonged (more than 10 minutes) or traumatic CPR, recent (within 2–4 weeks) internal bleeding, noncompressible vascular punctures, active diabetic retinopathy, pregnancy, active peptic ulcer disease, a history of severe hypertension, current use of anticoagulants (INR greater than 2.0–3.0), and (for streptokinase) prior allergic reaction or exposure to streptokinase or anistreplase within 2 years.

c. Fibrinolytic agents—The following fibrinolytic agents are available for acute MI and are characterized in Table 10–8.

Alteplase (recombinant tissue plasminogen activator; t-PA) results in about a 50% reduction in circulating fibrinogen. In the first GUSTO trial, which compared a 90-minute dosing of t-PA (with unfractionated heparin) with streptokinase, the 30-day mortality rate with t-PA was one absolute percentage point lower (one additional life saved per 100 patients treated), though there was also a small increase in the rate of intracranial hemorrhage. An angiographic substudy confirmed a higher 90-minute patency rate and a higher rate of normal (TIMI grade 3) flow in patients.

Reteplase is a recombinant deletion mutant of t-PA that is slightly less fibrin specific. In comparative trials, it appeared to have efficacy similar to that of alteplase, but it has a longer duration of action and can be administered as two boluses 30 minutes apart.

Tenecteplase (TNK-t-PA) is a genetically engineered substitution mutant of native t-PA that has reduced plasma clearance, increased fibrin sensitivity, and increased resistance to plasminogen activator inhibitor-1. It can be given as a single weight-adjusted bolus. In the ASSENT 2 trial, this agent was equivalent to t-PA with regard to efficacy and resulted in significantly less noncerebral bleeding.

Streptokinase, commonly used outside of the United States, is somewhat less effective at opening occluded arteries and less effective at reducing mortality. It is non–fibrin-specific, causes depletion of circulating fibrinogen, and has a tendency to induce hypotension, particularly if infused rapidly. This can be managed by slowing or interrupting the infusion and administering fluids. There is controversy as to whether adjunctive heparin is beneficial in patients given streptokinase, unlike its administration with the more clot-specific agents. Allergic reactions, including anaphylaxis, occur in 1–2% of patients, and this agent should generally not be administered to patients with prior exposure.

Table 10–8. Fibrinolytic therapy for acute MI.

	Alteplase; Tissue Plasminogen Activator (t-PA)	Reteplase	Tenecteplase (TNK-t-PA)	Streptokinase
Source	Recombinant DNA	Recombinant DNA	Recombinant DNA	Group C *Streptococcus*
Half-life	5 minutes	15 minutes	20 minutes	20 minutes
Usual dose	100 mg	20 units	40 mg	1.5 million units
Administration	Initial bolus of 15 mg, followed by 50 mg infused over the next 30 minutes and 35 mg over the following 60 minutes	10 units as a bolus over 2 minutes, repeated after 30 minutes	Single weight-adjusted bolus, 0.5 mg/kg	750,000 units over 20 minutes followed by 750,000 units over 40 minutes
Anticoagulation after infusion	Aspirin, 325 mg daily; heparin, 5000 units as bolus, followed by 1000 units/hour infusion, subsequently adjusted to maintain PTT 1.5–2 times control	Aspirin, 325 mg; heparin as with t-PA	Aspirin, 325 mg daily	Aspirin, 325 mg daily; there is no evidence that adjunctive heparin improves outcome following streptokinase
Clot selectivity	High	High	High	Low
Fibrinogenolysis	+	+	+	+++
Bleeding	+	+	+	+
Hypotension	+	+	+	+++
Allergic reactions	+	+	+	++
Reocclusion	10–30%	—	5–20%	5–20%
Approximate cost[1]	$10,560.43	$5964.98	$7462.63	Not available in the United States

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.
PTT, partial thromboplastin time.
Source: IBM Micromedex, Red Book (electronic version). IBM Watson Health, Greenwood Village, CO, USA. Available at https://www.micromedexsolutions.com (accessed April 8, 2020). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

(1) Selection of a fibrinolytic agent—In the United States, most patients are treated with alteplase, reteplase, or tenecteplase. The differences in efficacy between them are small compared with the potential benefit of treating a greater proportion of appropriate candidates in a more prompt manner. The principal objective should be to administer a thrombolytic agent within 30 minutes of presentation—or even during transport. The ability to administer tenecteplase as a single bolus is an attractive feature that may facilitate earlier treatment. The combination of a reduced-dose thrombolytic given with a platelet glycoprotein IIb/IIIa inhibitor does not reduce mortality but does cause a modest increase in bleeding complications.

(2) Postfibrinolytic management—After completion of the fibrinolytic infusion, aspirin (81–325 mg/day) and anticoagulation should be continued until revascularization or for the duration of the hospital stay (or up to 8 days). Anticoagulation with LMWH (enoxaparin or fondaparinux) is preferable to unfractionated heparin.

(a) Low-molecular-weight heparin—In the EXTRACT trial, enoxaparin significantly reduced death and MI at day 30 (compared with unfractionated heparin), at the expense of a modest increase in bleeding. In patients younger than age 75, enoxaparin was given as a 30-mg intravenous bolus and 1 mg/kg subcutaneously every 12 hours; in patients aged 75 years and older, it was given with no bolus and 0.75 mg/kg subcutaneously every 12 hours. This appeared to attenuate the risk of intracranial hemorrhage in older adults that had been seen with full-dose enoxaparin. Another antithrombotic option is fondaparinux, given at a dose of 2.5 mg subcutaneously once a day. There is no benefit of fondaparinux among patients undergoing primary PCI, and fondaparinux is not recommended as a sole anticoagulant during PCI due to risk of catheter thrombosis.

(b) Unfractionated heparin—Anticoagulation with intravenous heparin (initial dose of 60 units/kg bolus to a maximum of 4000 units, followed by an infusion of 12 units/kg/hour to a maximum of 1000 units/hour, then adjusted to maintain an aPTT of 50–75 seconds beginning with an aPTT drawn 3 hours after thrombolytic) is continued for at least 48 hours after alteplase, reteplase, or tenecteplase, and with continuation of an anticoagulant until revascularization (if performed) or until hospital discharge (or day 8).

The VALIDATE trial found no benefit to bivalirudin compared to unfractionated heparin regarding the outcome of death, MI, or major bleeding.

(c) Prophylactic therapy against GI bleeding—For all patients with STEMI treated with intensive antithrombotic therapy, prophylactic treatment with PPIs, or antacids and an H_2-blocker, is advisable. However, certain PPIs, such as omeprazole and esomeprazole, may decrease the clinical effect of clopidogrel; in such cases, pantoprazole may be a better PPI option.

3. Assessment of myocardial reperfusion, recurrent ischemic pain, reinfarction—Myocardial reperfusion can be recognized clinically by the early cessation of pain and the resolution of ST-segment elevation. Although at least 50% resolution of ST-segment elevation by 90 minutes may occur without coronary reperfusion, ST resolution is a strong predictor of better outcome. Even with anticoagulation, 10–20% of reperfused vessels will reocclude during hospitalization, although reocclusion and reinfarction appear to be reduced following intervention. Reinfarction, indicated by recurrence of pain and ST-segment elevation, can be treated by readministration of a thrombolytic agent or immediate angiography and PCI.

C. General Measures

Cardiac care unit monitoring should be instituted as soon as possible. Patients without complications can be transferred to a telemetry unit after 24 hours. Activity should initially be limited to bed rest but can be advanced within 24 hours. Progressive ambulation should be started after 24–72 hours if tolerated. For patients without complications, discharge by day 4 appears to be appropriate. Low-flow oxygen therapy (2–4 L/minute) should be given if oxygen saturation is reduced, but there is no value to routine use of oxygen.

D. Analgesia

An initial attempt should be made to relieve pain with sublingual nitroglycerin. However, if no response occurs after two or three tablets, intravenous opioids provide the most rapid and effective analgesia and may also reduce pulmonary congestion. Morphine sulfate, 4–8 mg, or meperidine, 50–75 mg, should be given. Subsequent small doses can be given every 15 minutes until pain abates.

NSAIDs, other than aspirin, should be avoided during hospitalization for STEMI due to increased risk of mortality, myocardial rupture, hypertension, heart failure, and kidney injury with their use.

E. Beta-Adrenergic Blocking Agents

Trials have shown modest short-term benefit from beta-blockers started during the first 24 hours after acute MI if there are no contraindications (metoprolol 25–50 mg orally twice daily). Aggressive beta-blockade can increase shock, with overall harm in patients with heart failure. Thus, early beta-blockade should be avoided in patients with any degree of heart failure, evidence of low output state, increased risk of cardiogenic shock, or other relative contraindications to beta-blockade. Carvedilol (beginning at 6.25 mg twice a day, titrated to 25 mg twice a day) was shown to be beneficial in the CAPRICORN trial following the acute phase of large MI.

F. Nitrates

Nitroglycerin is the agent of choice for continued or recurrent ischemic pain and is useful in lowering BP or relieving pulmonary congestion. However, routine nitrate administration is not recommended, since no improvement in outcome has been observed in the ISIS-4 or GISSI-3 trials. Nitrates should be avoided in patients who received phosphodiesterase inhibitors (sildenafil, vardenafil, and tadalafil) in the prior 24 hours.

G. ACE Inhibitors

A series of trials (SAVE, AIRE, SMILE, TRACE, GISSI-III, and ISIS-4) have shown both short- and long-term

improvement in survival with ACE inhibitor therapy. The benefits are greatest in patients with an EF of 40% or less, large infarctions, or clinical evidence of heart failure. Because substantial amounts of the survival benefit occur on the first day, ACE inhibitor treatment should be commenced early in patients without hypotension, especially patients with large or anterior MI. Given the benefits of ACE inhibitors for patients with vascular disease, it is reasonable to **use ACE inhibitors for *all* patients following STEMI who do not have contraindications.**

H. Angiotensin Receptor Blockers

Although there has been inconsistency in the effects of different ARBs on mortality for patients post-MI with heart failure and/or LV dysfunction, the VALIANT trial showed that valsartan 160 mg orally twice a day is *equivalent* to captopril in reducing mortality. Thus, valsartan should be used for all patients with ACE inhibitor intolerance, and is a reasonable, albeit more expensive, alternative to captopril. The combination of captopril and valsartan (at a reduced dose) was no better than either agent alone and resulted in more side effects.

I. Aldosterone Antagonists

The RALES trial showed that 25 mg of spironolactone can reduce the mortality rate of patients with advanced heart failure, and the EPHESUS trial showed a 15% relative risk reduction in mortality with eplerenone 25 mg daily for patients post-MI with LV dysfunction (LVEF of 40% or less) and either clinical heart failure or diabetes. Kidney dysfunction or hyperkalemia are contraindications, and patients must be monitored carefully for development of hyperkalemia.

J. Calcium Channel Blockers

There are no studies to support the routine use of calcium channel blockers in most patients with acute MI—and indeed, they have the potential to exacerbate ischemia and cause death from reflex tachycardia or myocardial depression. Long-acting calcium channel blockers should generally be reserved for management of hypertension or ischemia as second- or third-line medications after beta-blockers and nitrates.

K. Long-Term Antithrombotic Therapy

Discharge on aspirin, 81–325 mg/day, since it is highly effective, inexpensive, and well tolerated, is a key quality indicator of MI care. Patients who received a coronary stent should also receive a $P2Y_{12}$ inhibitor (see Antiplatelet therapy after drug-eluting or bare metal stents, above).

Patients who have received a coronary stent and who require warfarin anticoagulation present a particular challenge, since **"triple therapy"** with aspirin, clopidogrel, and warfarin has a high risk of bleeding. Triple therapy should be (1) limited to patients with a clear indication for warfarin (such as $CHADS_2$ score of 2 or more or a mechanical prosthetic valve), (2) used for the shortest period of time (such as 1 month after placement of bare metal stent; drug-eluting stents that would require longer clopidogrel duration should be avoided if possible), (3) used with low-dose aspirin and with strategies to reduce risk of bleeding (eg, PPIs for patients with a history of GI bleeding), and (4) used with consideration of a lower target anticoagulation intensity (INR 2.0–2.5, at least for the indication of atrial fibrillation) during the period of concomitant treatment with aspirin and $P2Y_{12}$ therapy. The PIONEER trial studied three treatment regimens for patients with atrial fibrillation who had coronary stent placement with a primary outcome of bleeding: (1) rivaroxaban 2.5 mg twice daily plus clopidogrel, (2) rivaroxaban 15 mg once daily plus clopidogrel, and (3) warfarin plus aspirin plus clopidogrel. There was less bleeding in the patients who received rivaroxaban plus clopidogrel than in those who received "triple therapy," although the trial was not powered to assess efficacy, and thus the low dose of rivaroxaban may be inadequate. Consensus statements recommend oral anticoagulation (with either warfarin or a DOAC) be combined with clopidogrel and with a relatively short duration of aspirin until hospital discharge up to 3 months for the typical patient with atrial fibrillation and coronary stents. Dabigatran, 110 mg and 150 mg, was also studied in patients with atrial fibrillation who underwent PCI. Dual therapy with dabigatran and clopidogrel was shown to be beneficial for bleeding compared to triple therapy, with similar rates of thrombotic cardiovascular events. However, there were too few thrombotic events to be certain about efficacy of discontinuing the aspirin, and there was a suggestion that MI and stent thrombosis occurred more often with the 110-mg dose of dabigatran than with clopidogrel alone. **Given the trial evidence to date, for a typical patient, it is reasonable to use a DOAC and clopidogrel and to discontinue aspirin at the time of hospital discharge or at 7 days after stenting.** The AUGUSTUS trial, which tested apixaban versus warfarin and aspirin versus placebo in a factorial trial, found that apixaban resulted in 31% less major and clinically relevant non major bleeding than warfarin for patients with atrial fibrillation and coronary stents or acute coronary syndromes or both. Avoiding aspirin, after an average of 6 days after the PCI, resulted in less bleeding and a nonsignificant increase in stent thrombosis. It is reasonable to stop aspirin at hospital discharge or at day 7 for patients with atrial fibrillation who are taking apixaban or warfarin at the time of discharge, although continuing aspirin for 1 month may reduce stent thrombosis.

L. Coronary Angiography

For patients who do not reperfuse based on lack of at least 50% resolution of ST elevation, **rescue angioplasty** should be performed and has been shown to reduce the composite risk of death, reinfarction, stroke, or severe heart failure. Patients treated with coronary angiography and PCI 3–24 hours after fibrinolytic therapy showed improved outcomes. Patients with recurrent ischemic pain prior to discharge should undergo catheterization and, if indicated, revascularization. PCI of a totally occluded infarct-related artery more than 24 hours after STEMI should generally not be performed in asymptomatic patients with one- or two-vessel disease without evidence of severe ischemia.

When to Refer

All patients with acute MI should be referred to a cardiologist.

Lopes RD et al; AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med. 2019;380:1509. [PMID: 30883055]

Complications

A variety of complications can occur after MI even when treatment is initiated promptly.

A. Postinfarction Ischemia

In clinical trials of thrombolysis, recurrent ischemia occurred in about one-third of patients, was more common following NSTEMI than after STEMI, and had important short- and long-term prognostic implications. Vigorous medical therapy should be instituted, including nitrates and beta-blockers as well as aspirin 81–325 mg/day, anticoagulant therapy (unfractionated heparin, enoxaparin, or fondaparinux), and clopidogrel (75 mg orally daily). Most patients with postinfarction angina—and all who are refractory to medical therapy—should undergo early catheterization and revascularization by PCI or CABG.

B. Arrhythmias

Abnormalities of rhythm and conduction are common.

1. Sinus bradycardia—This is most common in inferior infarctions or may be precipitated by medications. Observation or withdrawal of the offending agent is usually sufficient. If accompanied by signs of low cardiac output, atropine intravenously is usually effective. Temporary pacing is rarely required.

2. Supraventricular tachyarrhythmias—Sinus tachycardia is common and may reflect either increased adrenergic stimulation or hemodynamic compromise due to hypovolemia or pump failure. In the latter, beta-blockade is contraindicated. Supraventricular premature beats are common and may be premonitory for atrial fibrillation. Electrolyte abnormalities and hypoxia should be corrected and causative agents (especially aminophylline) stopped. Atrial fibrillation should be rapidly controlled or converted to sinus rhythm. Intravenous beta-blockers, such as metoprolol (2.5–5 mg intravenously every 2–5 minutes, maximum 15 mg over 10–minutes) or short-acting esmolol (50–200 mcg/kg/minute), are the agents of choice if cardiac function is adequate. Intravenous diltiazem (5–15 mg/hour) may be used if beta-blockers are contraindicated or ineffective. Electrical cardioversion (commencing with 100 J) may be necessary if atrial fibrillation is complicated by hypotension, heart failure, or ischemia, but the arrhythmia often recurs. Amiodarone (150 mg intravenous bolus and then 15–30 mg/hour intravenously, or rapid oral loading dose for cardioversion of 400 mg three times daily) may be helpful to restore or maintain sinus rhythm.

3. Ventricular arrhythmias—Ventricular arrhythmias are most common in the first few hours after infarction and are a marker of high risk. Ventricular premature beats may be premonitory for ventricular tachycardia or fibrillation, but generally should *not* be treated in the absence of frequent or sustained ventricular tachycardia. Lidocaine is *not* recommended as a prophylactic measure.

Sustained ventricular tachycardia should be treated with a 1 mg/kg bolus of lidocaine if the patient is stable or by electrical cardioversion (100–200 J) if not. If the arrhythmia cannot be suppressed with lidocaine, procainamide (100 mg boluses over 1–2 minutes every 5 minutes to a cumulative dose of 750–1000 mg) or intravenous amiodarone (150 mg over 10 minutes, which may be repeated as needed, followed by 360 mg over 6 hours and then 540 mg over 18 hours) should be initiated, followed by an infusion of 0.5 mg/minute (720 mg/24 hours). Ventricular fibrillation is treated electrically (300–400 J). All patients taking antiarrhythmics should be monitored with telemetry or ECGs during initiation. Unresponsive ventricular fibrillation should be treated with additional amiodarone and repeat cardioversion while CPR is administered.

Accelerated idioventricular rhythm is a regular, wide-complex rhythm at a rate of 60–120/minute. It may occur with or without reperfusion and should not be treated with antiarrhythmics, which could cause asystole.

4. Conduction disturbances—All degrees of AV block may occur in the course of acute MI. Block at the level of the AV node is more common than infranodal block and occurs in approximately 20% of inferior MIs. First-degree block is the most common and requires no treatment. Second-degree block is usually of the Mobitz type I form (Wenckebach), is often transient, and requires treatment only if associated with a heart rate slow enough to cause symptoms. Complete AV block occurs in up to 5% of acute inferior infarctions, usually is preceded by Mobitz I second-degree block, and generally resolves spontaneously, though it may persist for hours to several weeks. The escape rhythm originates in the distal AV node or AV junction and hence has a narrow QRS complex and is reliable, albeit often slow (30–50 beats/minute). Treatment is often necessary because of resulting hypotension and low cardiac output. Intravenous atropine (1 mg) usually restores AV conduction temporarily, but if the escape complex is wide or if repeated atropine treatments are needed, temporary ventricular pacing is indicated. The prognosis for these patients is only slightly worse than for patients in whom AV block does not develop.

In anterior infarctions, the site of block is distal, below the AV node, and usually a result of extensive damage of the His-Purkinje system and bundle branches. New first-degree block (prolongation of the PR interval) is unusual in anterior infarction; Mobitz type II AV block or complete heart block may be preceded by intraventricular conduction defects or may occur abruptly. The escape rhythm, if present, is an unreliable wide-complex idioventricular rhythm. Urgent ventricular pacing is mandatory, but even with successful pacing, morbidity and mortality are high because of the extensive myocardial damage. New conduction abnormalities, such as right or left bundle branch

block or fascicular blocks, may presage progression, often sudden, to second- or third-degree AV block. Temporary ventricular pacing is recommended for new-onset alternating bilateral bundle branch block, bifascicular block, or bundle branch block with worsening first-degree AV block. Patients with anterior infarction who progress to second- or third-degree block even transiently should be considered for insertion of a prophylactic permanent ventricular pacemaker before discharge.

C. Myocardial Dysfunction

Persons with hypotension not responsive to fluid resuscitation or refractory heart failure or cardiogenic shock should be considered for urgent echocardiography to assess left and right ventricular function and for mechanical complications, right heart catheterization, and continuous measurements of arterial pressure. These measurements permit the accurate assessment of volume status and may facilitate decisions about volume resuscitation, selective use of vasopressors and inotropes, and mechanical support.

1. Acute LV failure—Dyspnea, diffuse rales, and arterial hypoxemia usually indicate LV failure. General measures include supplemental oxygen to increase arterial saturation to above 95% and elevation of the trunk. Diuretics are usually the initial therapy unless RV infarction is present. Intravenous furosemide (10–40 mg) or bumetanide (0.5–1 mg) is preferred because of the reliably rapid onset and short duration of action of these medications. Higher dosages can be given if an inadequate response occurs. Morphine sulfate (4 mg intravenously followed by increments of 2 mg) is valuable in acute pulmonary edema.

Diuretics are usually effective; however, because most patients with acute infarction are not volume overloaded, the hemodynamic response may be limited and may be associated with hypotension. In mild heart failure, sublingual isosorbide dinitrate (2.5–10 mg every 2 hours) or nitroglycerin ointment (6.25–25 mg every 4 hours) may be adequate to lower pulmonary capillary wedge pressure (PCWP). In more severe failure, especially if cardiac output is reduced and BP is normal or high, sodium nitroprusside may be the preferred agent. It should be initiated only with arterial pressure monitoring; the initial dosage should be low (0.25 mcg/kg/minute) to avoid excessive hypotension, but the dosage can be increased by increments of 0.5 mcg/kg/minute every 5–10 minutes up to 5–10 mcg/kg/minute until the desired hemodynamic response is obtained. Excessive hypotension (mean BP less than 65–75 mm Hg) or tachycardia (greater than 10/minutes increase) should be avoided.

Intravenous nitroglycerin (starting at 10 mcg/minute) also may be effective but may lower PCWP with less hypotension. Oral or transdermal vasodilator therapy with nitrates or ACE inhibitors is often necessary after the initial 24–48 hours.

Inotropic agents should be avoided if possible, because they often increase heart rate and myocardial oxygen requirements and worsen clinical outcomes. Dobutamine has the best hemodynamic profile, increasing cardiac output and modestly lowering PCWP, usually without excessive tachycardia, hypotension, or arrhythmias. The initial dosage is 2.5 mcg/kg/minute, and it may be increased by similar increments up to 15–20 mcg/kg/minute at intervals of 5–10 minutes. Dopamine is more useful in the presence of hypotension, since it produces peripheral vasoconstriction, but it has a less beneficial effect on PCWP. Digoxin has not been helpful in acute infarction except to control the ventricular response in atrial fibrillation, but it may be beneficial if chronic heart failure persists.

2. Hypotension and shock—Patients with hypotension (systolic BP less than 90 mm Hg, individualized depending on prior BP) and signs of diminished perfusion (low urinary output, confusion, cold extremities) that does not respond to fluid resuscitation should be presumed to have cardiogenic shock and should be considered for urgent catheterization and revascularization. Sparing use of **intra-aortic balloon pump (IABP)** support and hemodynamic monitoring with a **PA catheter** can be considered, although these later measures have *not* been shown to improve outcome. Up to 20% will have findings indicative of intravascular hypovolemia (due to diaphoresis, vomiting, decreased venous tone, medications—such as diuretics, nitrates, morphine, beta-blockers, calcium channel blockers, and thrombolytic agents—and lack of oral intake). These should be treated with successive boluses of 100 mL of normal saline until PCWP reaches 15–18 mm Hg to determine whether cardiac output and BP respond. Pericardial tamponade due to hemorrhagic pericarditis (especially after thrombolytic therapy or CPR) or ventricular rupture should be considered and excluded by echocardiography if clinically indicated. RV infarction, characterized by a normal PCWP but elevated RA pressure, can produce hypotension. This is discussed below.

Most patients with cardiogenic shock will have moderate to severe LV systolic dysfunction, with a mean EF of 30% in the SHOCK trial. If hypotension is only modest (systolic pressure higher than 90 mm Hg) and the PCWP is elevated, diuretics should be administered. If the BP falls, inotropic support will need to be added. A large randomized trial showed *no benefit* of IABP support in cardiogenic shock.

Norepinephrine (0.1–0.5 mcg/kg/minute) is generally considered to be the most appropriate inotrope/vasopressor for cardiogenic shock based on limited randomized clinical trial evidence suggesting less arrhythmias and improved outcomes compared with dopamine. Dopamine is nonetheless also an option and can be initiated at a rate of 2–4 mcg/kg/minute and increased at 5-minute intervals to the appropriate hemodynamic end point. At dosages lower than 5 mcg/kg/minute, it improves renal blood flow; at intermediate dosages (2.5–10 mcg/kg/min), it stimulates myocardial contractility; at higher dosages (greater than 8 mcg/kg/minute), it is a potent alpha-1-adrenergic agonist. In general, BP and cardiac index rise, but PCWP does not fall. Dopamine may be combined with nitroprusside or dobutamine (see above for dosing), or the latter may be used in its place if hypotension is not severe.

Patients with cardiogenic shock not due to hypovolemia have a poor prognosis, with 30-day mortality rates of 40–80%. The IABP-SHOCK II trial found that the use of an IABP does not offer a mortality benefit at 30 days or 1 year,

compared with routine care with rapid revascularization, and is likely not helpful. Surgically implanted (or percutaneous) ventricular assist devices may be used in refractory cases. Emergent cardiac catheterization and coronary angiography followed by percutaneous or surgical revascularization offer the best chance of survival. Additionally, revascularization in shock should be aimed at the culprit artery only, avoiding multivessel PCI.

D. RV Infarction

RV infarction is present in one-third of patients with inferior wall infarction but is clinically significant in less than 50% of these. It presents as hypotension with relatively preserved LV function and should be considered whenever patients with inferior infarction exhibit low BP, raised venous pressure, and clear lungs. Hypotension is often exacerbated by medications that decrease intravascular volume or produce venodilation, such as diuretics, nitrates, and opioids. RA pressure and JVP are high, while PCWP is normal or low and the lungs are clear. The diagnosis is suggested by ST-segment elevation in right-sided anterior chest leads, particularly RV_4. The diagnosis can be confirmed by echocardiography or hemodynamic measurements. Treatment consists of fluid loading beginning with 500 mL of 0.9% saline over 2 hours to improve LV filling, and inotropic agents only if necessary.

E. Mechanical Defects

Partial or complete rupture of a papillary muscle or of the interventricular septum occurs in less than 1% of acute MIs and carries a poor prognosis. These complications occur in both anterior and inferior infarctions, usually 3–7 days after the acute event. They are detected by the appearance of a new systolic murmur and clinical deterioration, often with pulmonary edema. The two lesions are distinguished by the location of the murmur (apical versus parasternal) and by Doppler echocardiography. Hemodynamic monitoring is essential for appropriate management and demonstrates an increase in oxygen saturation between the RA and PA in VSD and, often, a large *v* wave with mitral regurgitation. Treatment by nitroprusside and, preferably, **intra-aortic balloon counterpulsation (IABC)** reduces the regurgitation or shunt, but surgical correction is mandatory. In patients remaining hemodynamically unstable or requiring continuous parenteral pharmacologic treatment or counterpulsation, early surgery is recommended, though mortality rates are high (15% to nearly 100%, depending on residual ventricular function and clinical status). Patients who are stabilized medically can have delayed surgery with lower risks (10–25%), although this may be due to the death of sicker patients, some of whom may have been saved by earlier surgery.

F. Myocardial Rupture

Complete rupture of the LV free wall occurs in less than 1% of patients and usually results in immediate death. It occurs 2–7 days postinfarction, usually involves the anterior wall, and is more frequent in older women. Incomplete or gradual rupture may be sealed off by the pericardium, creating a pseudoaneurysm. This may be recognized by echocardiography, radionuclide angiography, or LV angiography, often as an incidental finding. It demonstrates a narrow-neck connection to the LV. Early surgical repair is indicated, since delayed rupture is common.

G. LV Aneurysm

An LV aneurysm, a sharply delineated area of scar that bulges paradoxically during systole, develops in 10–20% of patients surviving an acute infarction. This usually follows anterior ST-elevation infarctions. Aneurysms are recognized by persistent ST-segment elevation (beyond 4–8 weeks), and a wide neck from the LV can be demonstrated by echocardiography, scintigraphy, or contrast angiography. They rarely rupture but may be associated with arterial emboli, ventricular arrhythmias, and heart failure. Surgical resection may be performed for these indications if other measures fail. The best results (mortality rates of 10–20%) are obtained when the residual myocardium contracts well and when significant coronary lesions supplying adjacent regions are bypassed.

H. Pericarditis

The pericardium is involved in approximately 50% of infarctions, but pericarditis is often not clinically significant. Twenty percent of patients with ST-elevation infarctions will have an audible friction rub if examined repetitively. Pericardial pain occurs in approximately the same proportion after 2–7 days and is recognized by its variation with respiration and position (improved by sitting). Often, no treatment is required, but aspirin (650 mg every 4–6 hours) will usually relieve the pain. Indomethacin and corticosteroids can cause impaired infarct healing and predispose to myocardial rupture, and therefore should generally be avoided in the early post-MI period. Likewise, anticoagulation should be used cautiously, since hemorrhagic pericarditis may result.

One week to 12 weeks after infarction, **Dressler syndrome** (post-MI syndrome) occurs in less than 5% of patients. This is an autoimmune phenomenon and presents as pericarditis with associated fever, leukocytosis, and, occasionally, pericardial or pleural effusion. It may recur over months. Treatment is the same as for other forms of pericarditis. A short course of nonsteroidal agents or corticosteroids may help relieve symptoms, but the use of nonsteroidal agents in the first several weeks after MI may impair infarct healing.

I. Mural Thrombus

Mural thrombi are common in large anterior infarctions but not in infarctions at other locations. Arterial emboli occur in approximately 2% of patients with known infarction, usually within 6 weeks. Anticoagulation with heparin followed by short-term (3-month) warfarin therapy (or DOAC therapy based on limited case report experience) results in clot resolution and prevents most emboli and should be considered in all patients with large anterior infarctions and evidence of LV thrombi. Mural thrombi can be detected by echocardiography or cardiac MRI. If the

thrombus is resolved at 3 months, then anticoagulation can be discontinued.

Postinfarction Management

After the first 24 hours, the focus of patient management is to prevent recurrent ischemia, improve infarct healing and prevent remodeling, and prevent recurrent vascular events. Patients with hemodynamic compromise, who are at high risk for death, need careful monitoring and management of volume status.

A. Risk Stratification

Risk stratification is important for the management of STEMI. GRACE and TIMI risk scores can be helpful tools. Patients with recurrent ischemia (spontaneous or provoked), hemodynamic instability, impaired LV function, heart failure, or serious ventricular arrhythmias should undergo cardiac catheterization (see Table 10–7). ACE inhibitor (or ARB) therapy is indicated in patients with clinical heart failure or LVEF of 40% or less. Aldosterone blockade is indicated for patients with an LVEF of 40% or less and either heart failure or diabetes mellitus.

For patients not undergoing cardiac catheterization, submaximal exercise (or pharmacologic stress testing for patients unable to exercise) before discharge or a maximal test after 3–6 weeks (the latter being more sensitive for ischemia) helps patients and clinicians plan the return to normal activity. Imaging in conjunction with stress testing adds additional sensitivity for ischemia and provides localizing information. Both exercise and pharmacologic stress imaging have successfully predicted subsequent outcome. One of these tests should be used prior to discharge in patients who have received thrombolytic therapy as a means of selecting appropriate candidates for coronary angiography.

B. Secondary Prevention

Postinfarction management should begin with identification and modification of risk factors. Treatment of hyperlipidemia and smoking cessation both prevent recurrent infarction and death. Statin therapy should be started before the patient is discharged from the hospital to reduce recurrent atherothrombotic events. BP control as well as cardiac rehabilitation and exercise are also recommended. They can be of considerable psychological benefit and appear to improve prognosis.

Beta-blockers improve survival rates, primarily by reducing the incidence of sudden death in high-risk subsets of patients, though their value may be less in patients without complications with small infarctions and normal exercise tests. While a variety of beta-blockers have been shown to be beneficial, for patients with LV dysfunction managed with contemporary treatment, carvedilol titrated to 25 mg orally twice a day has been shown to reduce mortality. Beta-blockers with intrinsic sympathomimetic activity have not proved beneficial in postinfarction patients.

Antiplatelet agents are beneficial; aspirin (75–100 mg daily, after the initial dose) and $P2Y_{12}$ inhibitor therapy for 1 year are recommended. Prasugrel provides further reduction in thrombotic outcomes compared with clopidogrel, at the cost of more bleeding, but is contraindicated for patients with prior stroke. Likewise, ticagrelor provides benefit over clopidogrel. Calcium channel blockers have *not* been shown to improve prognoses overall and should not be prescribed purely for secondary prevention. Antiarrhythmic therapy other than with beta-blockers has *not* been shown to be effective except in patients with symptomatic arrhythmias. Amiodarone has been studied in several trials of postinfarct patients with either LV dysfunction or frequent ventricular ectopy. Although survival was not improved, amiodarone was not harmful—unlike other agents in this setting. Therefore, it is the agent of choice for individuals with symptomatic postinfarction supraventricular arrhythmias. While implantable defibrillators improve survival for patients with postinfarction LV dysfunction and heart failure, the DINAMIT trial found no benefit to implantable defibrillators implanted in the 40 days following acute MI.

C. ACE Inhibitors and ARBs in Patients with LV Dysfunction

Patients who sustain substantial myocardial damage often experience subsequent progressive LV dilation and dysfunction, leading to clinical heart failure and reduced long-term survival. In patients with EFs less than 40%, long-term ACE inhibitor (or ARB) therapy prevents LV dilation and the onset of heart failure and prolongs survival. The HOPE trial, as well as an overview of trials of ACE inhibitors for secondary prevention, also demonstrated a reduction of approximately 20% in mortality rates and the occurrence of nonfatal MI and stroke with ramipril treatment of patients with coronary or peripheral vascular disease and without confirmed LV systolic dysfunction. Therefore, ACE inhibitor therapy should be strongly considered in this broader group of patients—and especially in patients with diabetes and those with even mild systolic hypertension, in whom the greatest benefit was observed (see Table 11–6).

D. Revascularization

The indications for CABG are similar to those for patients with chronic coronary syndromes, including left main stenosis and multivessel disease (particularly with type 2 diabetes or LV dysfunction, or both). For patients who have undergone primary PCI and have residual left main or multivessel disease, CABG may be appropriate, but the timing needs to take into account the high risk of stent thrombosis if $P2Y_{12}$ inhibitor therapy is interrupted. For patients with noninfarct-related CAD, stenting should generally be performed on these lesions prior to hospital discharge.

Ibanez B et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119. [PMID: 28886621]

DISORDERS OF RATE & RHYTHM

Abnormalities of cardiac rhythm and conduction can be symptomatic (syncope, near syncope, dizziness, fatigue, or palpitations) or asymptomatic. In addition, they can be lethal (sudden cardiac death) or dangerous to the extent that they reduce cardiac output, so that perfusion of the brain and myocardium is impaired. Stable supraventricular tachycardia (SVT) is generally well tolerated in patients without underlying heart disease but may lead to myocardial ischemia or heart failure in patients with coronary disease, valvular abnormalities, and systolic or diastolic myocardial dysfunction. Ventricular tachycardia, if prolonged, often results in hemodynamic compromise and may deteriorate into ventricular fibrillation if left untreated.

Whether slow heart rates produce symptoms at rest or with exertion depends on whether cerebral and peripheral perfusion can be maintained, which is generally a function of whether the patient is upright or supine and whether LV function is adequate to maintain stroke volume. If the heart rate abruptly slows, as with the onset of complete heart block or sinus arrest, syncope or convulsions (or both) may result. Unless a clear, reversible cause is found, most symptomatic patients require implantation of a permanent pacemaker.

The diagnosis of an abnormal tachyarrhythmia often can be made via cardiac monitoring, including in-hospital and ambulatory ECG monitoring, event recorders, continuous mobile cardiac telemetry, or implantable loop recorders. Additionally, optic sensors on wearable devices, such as smartwatches, utilize a passive irregular pulse notification algorithm to identify possible arrhythmia, with a positive predictive value for detection of atrial fibrillation of approximately 70%. Devices, such as certain Apple Watches and the AliveCor device, can record actual ECGs of rhythm that can be transmitted to health care providers. More invasive testing, including catheter-based electrophysiologic studies (to assess sinus node function, AV conduction, and inducibility of arrhythmias), and tests of autonomic nervous system function (tilt-table testing) can also be performed.

Treatment of tachyarrhythmias varies and can include modalities such as antiarrhythmic medications and more invasive techniques such as catheter ablation.

Antiarrhythmic Medications

Antiarrhythmic medications are frequently used to treat arrhythmias, but have variable efficacy and produce frequent side effects (Table 10–9). They are often divided into classes based on their electropharmacologic actions and many of these medications have multiple actions. The most frequently used classification scheme is the **Vaughan-Williams,** which consists of four classes.

Class I agents block membrane sodium channels. Three subclasses are further defined by the effect of the agents on the Purkinje fiber action potential. **Class Ia** medications (ie, quinidine, procainamide, disopyramide) slow the rate of rise of the action potential (V_{max}) and prolong its duration, thus slowing conduction and increasing refractoriness (moderate depression of phase 0 upstroke of the action potential). **Class Ib** agents (ie, lidocaine, mexiletine) shorten action potential duration; they do not affect conduction or refractoriness (minimal depression of phase 0 upstroke of the action potential). **Class Ic** agents (ie, flecainide, propafenone) prolong V_{max} and slow repolarization, thus slowing conduction and prolonging refractoriness, but more so than class Ia medications (maximal depression of phase 0 upstroke of the action potential).

Class II agents are the beta-blockers, which decrease automaticity, prolong AV conduction, and prolong refractoriness.

Class III agents (ie, amiodarone, dronedarone, sotalol, dofetilide, ibutilide) block potassium channels and prolong repolarization, widening the QRS and prolonging the QT interval. They decrease automaticity and conduction and prolong refractoriness.

Class IV agents are the calcium channel blockers, which decrease automaticity and AV conduction.

There are some antiarrhythmic agents that do not fall into one of these categories. The most frequently used are digoxin and adenosine. Digoxin inhibits the Na^+, K^+-ATPase pump. Digoxin prolongs AV nodal conduction and the AV nodal refractory period, but it shortens the action potential and decreases the refractoriness of the ventricular myocardium and Purkinje fibers. Adenosine can block AV nodal conduction and shortens atrial refractoriness.

Although the in vitro electrophysiologic effects of most of these agents have been defined, their use remains largely empiric. **All can exacerbate arrhythmias (proarrhythmic effect), and many depress LV function.**

The risk of antiarrhythmic agents has been highlighted by many studies, most notably the Coronary Arrhythmia Suppression Trial (CAST), in which two class Ic agents (flecainide, encainide) and a class Ia agent (moricizine) increased mortality rates in patients with asymptomatic ventricular ectopy after MI. Class Ic antiarrhythmic agents should therefore *not* be used in patients with prior MI or structural heart disease.

The use of antiarrhythmic agents for specific arrhythmias is discussed below.

Catheter Ablation for Cardiac Arrhythmias

Catheter ablation has become the primary modality of therapy for many symptomatic supraventricular arrhythmias, including AV nodal reentrant tachycardia, tachycardias involving accessory pathways, paroxysmal atrial tachycardia, and atrial flutter. Catheter ablation of atrial fibrillation is more complex and usually involves complete electrical isolation of the pulmonary veins (which are often the sites of initiation of atrial fibrillation) or placing linear lesions within the atria to prevent propagation throughout the atrial chamber. This technique is considered a reasonable therapy for symptomatic patients with medication-refractory atrial fibrillation or as an alternative to long-term antiarrhythmic medication treatment. Catheter ablation of ventricular arrhythmias has proved more difficult, but experienced centers have demonstrated reasonable success with all types of ventricular tachycardias including bundle-branch reentry, tachycardia originating in the ventricular outflow tract or papillary muscles, tachycardias originating in the specialized conduction system (fascicular

Table 10–9. Antiarrhythmic medications (listed in alphabetical order within class).

Agent	Intravenous Dosage	Oral Dosage	Therapeutic Plasma Level	Route of Elimination	Side Effects
Class Ia: Action: Sodium channel blockers: Depress phase 0 depolarization; slow conduction; prolong repolarization.					
Indications: Supraventricular tachycardia, ventricular tachycardia, symptomatic ventricular premature beats.					
Disopyramide		Immediate release: 100–200 mg every 6 hours Sustained release: 200–400 mg every 12 hours	2–8 mg/mL	Renal	Urinary retention, dry mouth, markedly ↓ LVF, QT prolongation
Procainamide	Loading: 10–17 mg/kg at 20–50 mg/minute Maintenance: 1–4 mg/minute	50 mg/kg/day in divided doses every 4 hours (short-acting)	4–10 mg/mL; NAPA (active metabolite), 10–20 mcg/mL	Renal	
Quinidine	6–10 mg/kg (intramuscularly or intravenously) over 20 minutes (rarely used parenterally)	324–648 mg every 8 hours	2–5 mg/mL	Hepatic	GI, ↓ LVF, ↑ Dig
Class Ib: Action: Shorten repolarization.					
Indications: Ventricular tachycardia, prevention of ventricular fibrillation, symptomatic ventricular premature beats.					
Lidocaine	Loading: 1 mg/kg Maintenance: 1–4 mg/minute		1–5 mg/mL	Hepatic	CNS, GI, ↓ LVF
Mexiletine		100–300 mg every 8–12 hours; maximum: 1200 mg/day	0.5–2 mg/mL	Hepatic	CNS, GI, leukopenia
Class Ic: Action: Depress phase 0 repolarization; slow conduction. (Propafenone is a weak calcium channel blocker and beta-blocker and prolongs action potential and refractoriness.)					
Indications: Ventricular tachycardia (in the absence of structural heart disease), refractory supraventricular tachycardia.					
Flecainide		50–150 mg twice daily	0.2–1 mg/mL	Hepatic	CNS, GI, AFL with 1:1 conduction, ventricular pro-arrhythmia
Propafenone		150–300 mg every 8–12 hours	Note: Active metabolites	Hepatic	CNS, GI, AFL with 1:1 conduction, ventricular pro-arrhythmia
Class II: Action: Beta-blockers, slow AV conduction.					
Indications: Supraventricular tachycardia, ventricular tachycardia, symptomatic ventricular premature beats, long QT syndrome.					
Esmolol	Loading: 500 mcg/kg over 1–2 minutes Maintenance: 50 mcg/kg/minute	Other beta-blockers may be used concomitantly	Not established	Hepatic	↓ LVF, bradycardia, AV block
Metoprolol	5 mg every 5 minutes up to 3 doses	25–200 mg daily	Not established	Hepatic	↓ LVF, bradycardia, AV block, fatigue
Propranolol	1–3 mg every 5 minute up to total of 5 mg	40–320 mg in 1–4 doses daily (depending on preparation)	Not established	Hepatic	↓ LVF, bradycardia, AV block, bronchospasm
Class III: Action: Prolong action potential.					
Indications: *Amiodarone:* refractory ventricular tachycardia, supraventricular tachycardia, prevention of ventricular tachycardia, atrial fibrillation, ventricular fibrillation; *Dofetilide:* atrial fibrillation and flutter; *Dronedarone:* atrial fibrillation (not persistent); *Ibutilide:* conversion of atrial fibrillation and flutter; *Sotalol:* ventricular tachycardia, atrial fibrillation.					
Amiodarone	150–300 mg infused rapidly, followed by 1 mg/minute infusion for 6 hours and then 0.5 mg/ minute for 18 hours	800–1600 mg/day for 7–14 days; maintain at 100–400 mg/day	1–5 mg/mL	Hepatic	Pulmonary fibrosis, hypothyroidism, hyperthyroidism, photosensitivity, corneal and skin deposits, hepatitis, ↑ Dig, neurotoxicity, GI

(*continued*)

Table 10–9. Antiarrhythmic medications (listed in alphabetical order within class). (continued)

Agent	Intravenous Dosage	Oral Dosage	Therapeutic Plasma Level	Route of Elimination	Side Effects
Dofetilide		125–500 mcg every 12 hours		Renal (dose must be reduced with kidney dysfunction)	Torsades de pointes in 3%; interaction with cytochrome P-450 inhibitors
Dronedarone		400 mg twice daily		Hepatic (contraindicated in severe impairment)	QTc prolongation, HF. Contraindicated in HF (NYHA class IV or recent decompensation), persistent AF
Ibutilide	1 mg over 10 minutes, followed by a second infusion of 0.5–1 mg over 10 minutes			Hepatic and renal	Torsades de pointes in up to 5% of patients within 3 hours after administration; patients must be monitored with defibrillator nearby
Sotalol	75 mg every 12 hours	80–160 mg every 12 hours (maximum 320 mg daily)		Renal (dosing interval should be extended if creatinine clearance is < 60 mL/minute)	Early incidence of torsades de pointes, ↓ LVF, bradycardia, fatigue (and other side effects associated with beta-blockers)
Class IV: Action: Slow calcium channel blockers.					
Indications: Supraventricular tachycardia, ventricular tachycardia (outflow tract, idiopathic).					
Diltiazem	0.25 mg/kg over 2 minutes; second 0.35-mg/kg bolus after 15 minutes if response is inadequate; infusion rate, 5–15 mg/hours	120–360 mg daily in 1–3 doses depending on preparation		Hepatic metabolism, renal excretion	Hypotension, ↓ LVF, bradycardia
Verapamil	2.5 mg bolus followed by additional boluses of 2.5–5 mg every 1–3 minutes; total 20 mg over 20 minutes; maintain at 5 mg/kg/minute	80–120 mg every 6–8 hours; 240–480 mg once daily with sustained-release preparation	0.1–0.15 mg/mL	Hepatic	Hypotension, ↓ LVF, constipation, ↑ Dig
Miscellaneous: Indications: Supraventricular tachycardia.					
Adenosine	6 mg rapidly followed by 12 mg after 1–2 minutes if needed; use half these doses if administered via central line			Adenosine receptor stimulation, metabolized in blood	Transient flushing, dyspnea, chest pain, AV block, sinus bradycardia; effect ↓ by theophylline, ↑ by dipyridamole
Digoxin	0.5 mg over 20 minutes followed by increment of 0.25 or 0.125 mg to 1–1.5 mg over 24 hours	1–1.5 mg over 24–36 hours in 3 or 4 doses; maintenance, 0.125–0.5 mg/day	0.7–2 mg/mL	Renal	AV block, arrhythmias, GI, visual changes
Ivabradine		5–7.5 mg every 12 hours		Renal and fecal	Bradycardia, phosphenes (visual brightness)

AF, atrial fibrillation; AV, atrioventricular; Dig, elevation of serum digoxin level; HF, heart failure; ↓LVF, reduced LV function; NAPA, *N*-acetylprocainamide; NYHA, New York Heart Association.

ventricular tachycardia), and ventricular tachycardias occurring in patients with ischemic or dilated cardiomyopathy. Ablation of many of these arrhythmias can be performed from the endocardial surface via endovascular catheter placement or on the epicardial surface of the heart via a percutaneous subxiphoid approach.

Catheter ablation has also been successfully performed for the treatment of ventricular fibrillation when a uniform premature ventricular contraction (PVC) can be identified. In addition, patients with symptomatic PVCs or PVCs occurring at a high enough burden to result in a cardiomyopathy (usually more than 10,000/day) may be considered for catheter ablation as well.

Catheter ablation procedures are generally safe, with an overall major complication rate ranging from 1% to 5%. Major vascular damage during catheter insertion occurs in less than 2% of patients. There is a low incidence of perforation of the myocardial wall resulting in pericardial tamponade. Sufficient damage to the AV node to require permanent cardiac pacing occurs in less than 1% of patients. When transseptal access through the interatrial septum or retrograde LV catheterization is required, additional potential complications include damage to the heart valves, damage to a coronary artery, or systemic emboli. A rare but potentially fatal complication after catheter ablation of atrial fibrillation is the development of an atrioesophageal fistula resulting from ablation on the posterior wall of the LA just overlying the esophagus, estimated to occur in less than 0.1% of procedures.

Calkins H et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace. 2018;20:e1. [PMID: 29016840]

SINUS ARRHYTHMIA, BRADYCARDIA, & TACHYCARDIA

ESSENTIALS OF DIAGNOSIS

- Wide variation in sinus rate is common in young, healthy individuals and generally not pathologic.
- Symptomatic bradycardia may require permanent pacemaker implantation, especially in the elderly or patients with underlying heart disease.
- Sinus tachycardia is usually secondary to another underlying process (ie, fever, pain, anemia, alcohol withdrawal).
- Sick sinus syndrome manifests as sinus bradycardia, pauses, or inadequate heart rate response to physiologic demands (chronotropic incompetence).

General Considerations

Sinus arrhythmia is an irregularity of the normal heart rate defined as variation in the PP interval of more than 120 msec. This occurs commonly in young, healthy people due to changes in vagal influence on the sinus node during respiration (phasic) or independent of respiration (nonphasic). This is generally *not* a pathologic arrhythmia and requires no specific cardiac evaluation.

Sinus bradycardia is defined as a heart rate slower than 60 beats/minute and may be due to increased vagal influence on the normal sinoatrial pacemaker or organic disease of the sinus node. In healthy individuals, and particularly in well-trained athletes, sinus bradycardia to rates of 50 beats/minute or lower especially during sleep is a normal finding. However, in elderly patients and individuals with heart disease sinus bradycardia may be an indication of true sinus node pathology. When the sinus rate slows severely, the atrial-nodal junction or the nodal-His bundle junction may assume pacemaker activity for the heart, usually at a rate of 35–60 beats/minute.

Sinus tachycardia is defined as a heart rate faster than 100 beats/minute that is caused by rapid impulse formation from the sinoatrial node. It is a normal physiologic response to exercise or other conditions in which catecholamine release is increased. The rate infrequently exceeds 160 beats/minute but may reach 180 beats/minute in young persons. The onset and termination are usually gradual, in contrast to paroxysmal supraventricular tachycardia (PSVT) due to reentry. In rare instances, otherwise healthy individuals may present with "inappropriate" sinus tachycardia where persistently elevated basal heart rates are not in-line with physiologic demands. Long-term consequences of this disorder are few.

Sick sinus syndrome is a broad diagnosis applied to patients with sinus arrest, sinoatrial exit block (recognized by a pause equal to a multiple of the underlying PP interval or progressive shortening of the PP interval prior to a pause), or persistent sinus bradycardia. A common presentation in elderly patients is of recurrent SVTs (often atrial fibrillation) accompanied by bradyarrhythmias (**"tachy-brady syndrome"**). The long pauses that often follow the termination of tachycardia cause the associated symptoms. Sick sinus syndrome may also manifest as **chronotropic incompetence,** defined as an inappropriate heart rate response to the physiologic demands of exercise or stress, and is an underrecognized cause of poor exercise tolerance.

Clinical Findings

In most patients, sinus arrhythmia (bradycardia or tachycardia) does not cause symptoms in the absence of underlying cardiac disease or other comorbidities. When severe sinus bradycardia results in low cardiac output, however, patients may complain of weakness, confusion, or syncope if cerebral perfusion is impaired. Atrial, junctional, and ventricular ectopic rhythms are more apt to occur with slow sinus rates. Sinus bradycardia is often exacerbated by medications (digitalis, calcium channel blockers, beta-blockers, sympatholytic agents, antiarrhythmics), and nonessential agents that may be responsible should be withdrawn prior to making the diagnosis.

Sinus tachycardia is most often *a normal response* to conditions that require an increase in cardiac output, including fever, pain, anxiety, anemia, heart failure, hypovolemia, or thyrotoxicosis. Alcohol and alcohol withdrawal are common causes of sinus tachycardia and other

supraventricular arrhythmias. In patients with underlying cardiac disease, sinus tachycardia may cause dyspnea or chest pain due to increased myocardial oxygen demand or reduced coronary artery blood flow.

Symptoms from sinus node dysfunction are nonspecific and may be due to other causes. It is therefore essential that symptoms be demonstrated to coincide temporally with arrhythmias. This may require prolonged ambulatory monitoring or the use of an event recorder.

Treatment

Asymptomatic patients generally do *not* require treatment. For symptomatic patients with bradycardia or sick sinus syndrome, implantation of a permanent pacemaker is usually indicated. In patients without evidence of AV nodal or bundle branch conduction abnormality, a single chamber atrial pacemaker is reasonable. Based on the results of several randomized controlled trials, *atrial-based pacing (single or dual chamber) is superior to ventricular only pacing for patients with sinus node dysfunction.* When a dual-chamber pacemaker is implanted for sinus node dysfunction with intact AV conduction, unnecessary ventricular pacing should be avoided because it may exacerbate heart failure, especially in patients with preexisting LV dysfunction. In most situations, sinus tachycardia will improve or resolve with treatment of the underlying cause. Inappropriate sinus tachycardia in the presence of symptoms (palpitations, dizziness, exertional intolerance) can be treated with a trial of beta-blockers or calcium channel blockers although treatment is often challenging. Ivabradine (5–7.5 mg twice daily), a selective inhibitor of the potassium funny channel (I_f) specific to the sinus node, may be an effective treatment option.

When to Refer

Patients with symptoms related to bradycardia or tachycardia when reversible etiologies have been excluded.

Kusumoto FM et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2019;16:e128. [PMID: 30412778]

AV BLOCK

ESSENTIALS OF DIAGNOSIS

- Conduction disturbance between the atrium and ventricle that can be physiologic (due to enhanced vagal tone) or pathologic.
- Block occurs in the AV node (first-degree, second-degree Mobitz type I) or below the AV node (second-degree Mobitz type II, third-degree).
- Symptomatic AV block or block below the AV node in the absence of a reversible cause usually warrants permanent pacemaker implantation.

General Considerations

AV block can be physiologic (due to increased vagal tone) or pathologic (due to underlying heart disease such as ischemia, myocarditis, fibrosis of the conduction system, or after cardiac surgery). AV block is categorized as **first-degree** (PR interval greater than 200 msec with all atrial impulses conducted), **second-degree** (intermittent blocked beats), or **third-degree** (complete heart block, in which no atrial impulses are conducted to the ventricles). Second-degree AV block is further subclassified into **Mobitz type I (Wenckebach),** in which the AV conduction time (PR interval) progressively lengthens before the blocked beat, and **Mobitz type II,** in which there are intermittently non-conducted atrial beats not preceded by lengthening AV conduction. When only 2:1 AV block is present on the ECG, the differentiation between Mobitz type I or Mobitz type II is more difficult. If the baseline PR interval is prolonged (greater than 200 msec) or the width of the QRS complex is narrow (less than 120 msec), the block is usually nodal (Mobitz type I); if the QRS complex is wide (greater than or equal to 120 msec), the block is more likely infranodal (Mobitz type II).

AV dissociation occurs when an intrinsic ventricular pacemaker (accelerated idioventricular rhythm, ventricular premature beats, or ventricular tachycardia) is firing at a rate faster than or close to the sinus rate, such that atrial impulses arriving at the AV node when it is refractory may not be conducted. This phenomenon does not necessarily indicate AV block. No treatment is required aside from management of the causative arrhythmia.

Clinical Findings

The clinical presentation of first-degree and Mobitz type I block is typically benign and rarely produces symptoms. Normal, physiologic block of this type occurs in response to increases in parasympathetic output. This is commonly seen during sleep, with carotid sinus massage, or in well-trained athletes. It may also occur as a medication effect (calcium channel blockers, beta-blockers, digitalis, or antiarrhythmics). Pathologic causes, including myocardial ischemia or infarction (discussed earlier), inflammatory processes (ie, Lyme disease), fibrosis, calcification, or infiltration (ie, amyloidosis or sarcoidosis), should be excluded.

Mobitz type II block and complete (third-degree) heart block are almost always due to pathologic disease involving the infranodal conduction system, and symptoms including fatigue, dyspnea, presyncope or syncope are common. With complete heart block, where no atrial impulses reach the ventricle, the ventricular escape rate is usually slow (less than 50 beats/minute) and severity of symptoms may vary depending on the rate and stability of the escape rhythm. As for lesser degrees of AV block, pathologic causes should be explored.

Intraventricular conduction block is relatively common and may be transient (ie, related to increases in heart rate) or permanent. Right bundle branch block is often seen in patients with structurally normal hearts. The left bundle is composed of two components (anterior and posterior fascicles) and left bundle branch block is more often

a marker of underlying cardiac disease, including ischemic heart disease, inflammatory or infiltrative disease, cardiomyopathy, and valvular heart disease. In asymptomatic patients with bifascicular block (block in two of three infranodal components—right bundle, left anterior, and left posterior fascicle), the incidence of occult complete heart block or progression to it is low (1% annually).

Treatment

Asymptomatic patients with first- or second-degree Mobitz type I AV block do not require any specific therapy. Patients should undergo treatment of any potentially reversible cause (ie, myocardial ischemia or medication effect). Symptomatic patients with any degree of heart block should be treated urgently with atropine (initial dose 0.5 mg given intravenously) or temporary pacing (transcutaneous or transvenous). The indications for permanent pacing are symptomatic bradyarrhythmias with any degree of AV block or asymptomatic high-degree AV block (second-degree Mobitz type II or third-degree heart block) not attributable to a reversible or physiologic cause. Patients with presumed cardiac syncope with normal heart rates and rhythm but bifascicular or trifascicular block on ECG should also be considered for permanent pacing.

A *standardized nomenclature for pacemaker generators* is used, usually consisting of four letters. The first letter refers to the chamber that is paced (A, atrium; V, ventricle; D, dual [for both]). The second letter refers to the chamber that is sensed (also A, V, or D). An additional option (O) indicates absence of sensing. The third letter refers to how the pacemaker responds to a sensed event (I, inhibition by a sensed impulse; T, triggering by a sensed impulse; D, dual modes of response; O, no response to sensed impulse). The fourth letter refers to the programmability or rate response capacity (R, rate modulation), a function that can increase the pacing rate in response to motion or respiratory rate when the intrinsic heart rate is inappropriately low.

A dual-chamber pacemaker that senses and paces in both chambers is the most physiologic approach to pacing patients who remain in sinus rhythm. **AV synchrony** is particularly important in patients in whom atrial contraction produces a substantial augmentation of stroke volume. For patients in permanent atrial fibrillation who require pacing for symptomatic bradycardia or pauses, catheter-based implantation of a leadless pacemaker directly to the RV endocardium may be considered. In patients with complete heart block with LV systolic dysfunction, implantation of a pacemaker capable of direct capture of the native specialized conduction system (His bundle or left bundle) or simultaneous left and right ventricular pacing (CRT-P) may be indicated. Complications from pacemaker implantation include infection, hematoma, cardiac perforation, pneumothorax, and lead dislodgement.

When to Refer

Patients with symptomatic AV block (any degree) or asymptomatic high-degree (second-degree Mobitz type II or third-degree) AV block after reversible causes have been excluded.

Upadhyay GA et al; His-SYNC Investigators. His corrective pacing or biventricular pacing for cardiac resynchronization in heart failure. J Am Coll Cardiol. 2019;74:157. [PMID: 31078637]

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

ESSENTIALS OF DIAGNOSIS

- Rapid, regular tachycardia most commonly seen in young adults and characterized by abrupt onset and offset.
- QRS duration narrow (< 120 msec) except in the presence of bundle branch block or accessory pathway.
- Often responsive to vagal maneuvers, AV nodal blockers, or adenosine. Cardioversion rarely required.

General Considerations

PSVT is an intermittent arrhythmia that is characterized by a sudden onset and offset and a regular ventricular response. Episodes may last from a few seconds to several hours or longer. PSVT often occurs in patients without structural heart disease. The most common mechanism for PSVT is *reentry*, which may be initiated or terminated by a fortuitously timed atrial or ventricular premature beat. The reentrant circuit usually involves dual pathways (a slow and a fast pathway) within the AV node; this is referred to as **AV nodal reentrant tachycardia (AVNRT)** and accounts for 60% of cases of PSVT. Less commonly (30% of cases), reentry is due to an *accessory pathway* between the atria and ventricles, referred to as **atrioventricular reciprocating tachycardia (AVRT)**. The pathophysiology and management of arrhythmias due to accessory pathways differ in important ways and are discussed separately below.

Clinical Findings

A. Symptoms and Signs

Symptoms of PSVT can be quite variable depending on the degree of heart rate elevation, resultant hypotension, or presence of other comorbidities. Symptoms may include palpitations, diaphoresis, dyspnea, dizziness, and mild chest pain (even in the absence of associated CHD). Syncope is rare.

B. ECG

Obtaining a 12-lead ECG when feasible is important to help determine the tachycardia mechanism. The QRS duration will be narrow (less than 120 ms) except in cases of PSVT with aberrant conduction (left bundle branch block, right bundle branch block, or antegrade conducting accessory pathway). The heart rate is regular and is usually 160–220 beats/minute but may be greater than 250 beats/minute. The P wave usually differs in contour from sinus beats and is often simultaneous with or just after the QRS complex.

Treatment

In the absence of structural heart disease, serious effects are rare, and most episodes resolve spontaneously. Particular effort should be made to terminate the episode quickly if cardiac failure, syncope, or anginal pain develops or if there is underlying cardiac or (particularly) coronary disease. Because reentry is the most common mechanism for PSVT, effective therapy requires that conduction be interrupted at some point in the reentry circuit and the vast majority of these circuits involve the AV node.

A. Mechanical Measures

A variety of maneuvers have been used to interrupt episodes, and patients may learn to perform these themselves. These maneuvers result in an acute increase in vagal tone and include the Valsalva maneuver, lowering the head between the knees, coughing, splashing cold water on the face, and breath holding. The **Valsalva maneuver** is performed with the patient semirecumbent (45 degrees), exerting around 40 mm Hg of intrathoracic pressure (by blowing through a 10 mL syringe) for at least 15 seconds. Moving the patient supine immediately following the strain maneuver and passively raising their legs for an additional 15 seconds may increase effectiveness of the maneuver. **Carotid sinus massage** is an additional technique often performed by clinicians but should be avoided if the patient has a carotid bruit. Firm but gentle pressure and massage are applied first over the right carotid sinus for 10–20 seconds and, if unsuccessful, then over the left carotid sinus. Pressure should not be exerted on both sides at the same time. **Facial contact with cold water** may cause transient bradycardia and termination of PSVT, a phenomenon known as the diving reflex. When performed properly, these maneuvers result in abrupt termination of the arrhythmia in 20–50% of cases.

B. Medication Therapy

If mechanical measures fail to terminate the arrhythmia, pharmacologic agents should be tried. **Intravenous adenosine** is recommended as the first-line agent due to its brief duration of action and minimal negative inotropic activity (Table 10–9). Because the half-life of adenosine is less than 10 seconds, the medication is given rapidly (in 1–2 seconds) as a 6 mg bolus followed by 20 mL of fluid. If this regimen is unsuccessful at terminating the arrhythmia, a second higher dose (12 mg) may be given. Adenosine causes block of electrical conduction through the AV node and results in termination of PSVT in approximately 90% of cases. Minor side effects are common and include transient flushing, chest discomfort, nausea, and headache. Adenosine may excite both atrial and ventricular tissue causing atrial fibrillation (in up to 12% of patients) or rarely ventricular arrhythmias and therefore administration should be performed with continuous cardiac monitoring and availability of an external defibrillator. Adenosine must also be used with caution in patients with reactive airways disease because it can promote bronchospasm.

When adenosine fails to terminate the arrhythmia or if a contraindication to its use is present, **intravenous calcium channel blockers**, including verapamil and diltiazem, may be used (Table 10–9). Verapamil in particular has been shown to be as effective at terminating PSVT in the acute setting (approximately 90%) as adenosine. Calcium channel blockers should be used with caution in patients with heart failure due to their negative inotropic effects. Their longer half-life compared to adenosine may result in prolonged hypotension despite restoration of normal rhythm. Etripamil, a short-acting calcium-channel blocker that is self-administered intranasally, results in rapid conversion of PSVT in preliminary studies and phase 3 trials are ongoing.

Intravenous beta-blockers include esmolol (a very short-acting beta-blocker), propranolol, and metoprolol. While beta-blockers cause less myocardial depression than calcium channel blockers, the evidence of their effectiveness to terminate PSVT is limited. Although **intravenous amiodarone** is safe, it is usually not required and often ineffective for treatment of these arrhythmias.

C. Cardioversion

If the patient is hemodynamically unstable or if adenosine, beta-blockers, and calcium channel blockers are contraindicated or ineffective, synchronized electrical cardioversion (beginning at 100 J) should be performed.

Prevention

A. Catheter Ablation

Because of concerns about the safety and the intolerability of antiarrhythmic medications, **radiofrequency ablation is the preferred approach to patients with recurrent symptomatic reentrant PSVT,** whether it is due to dual pathways within the AV node or to accessory pathways.

B. Medications

AV nodal blocking agents are the medications of choice as first-line medical therapy (Table 10–9). Beta-blockers or nondihydropyridine calcium channel blockers, such as diltiazem and verapamil, are typically used first. Patients who do not respond to agents that increase refractoriness of the AV node may be treated with antiarrhythmics. The class Ic agents (flecainide, propafenone) can be used in patients without underlying structural heart disease. In patients with evidence of structural heart disease, class III agents, such as sotalol or amiodarone, should be used because of the lower incidence of ventricular proarrhythmia during long-term therapy.

When to Refer

All patients with sustained or symptomatic PSVT should be referred to a cardiologist or cardiac electrophysiologist for long-term treatment options (including observation, pharmacotherapy, or ablation).

Page RL et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2016;67:e27. [PMID: 26409259]

PSVT DUE TO ACCESSORY AV PATHWAYS (Preexcitation Syndromes)

ESSENTIALS OF DIAGNOSIS

- Two classic features of Wolff-Parkinson-White (WPW) pattern on ECG are short PR interval and wide, slurred QRS complex due to manifest preexcitation (delta wave).
- Most patients with WPW pattern do not have clinical history of arrhythmia but have a higher risk of sudden cardiac death due to rapidly conducted atrial fibrillation through the accessory pathway.
- Risk factors include age younger than 20, history of tachycardia, and rapid conduction properties at electrophysiologic testing.

General Considerations

Accessory pathways or bypass tracts between the atrium and the ventricle bypass the compact AV node and can predispose to reentrant arrhythmias, such as AVRT and atrial fibrillation. When direct AV connections conduct antegrade (manifest preexcitation) they produce a classic **WPW pattern** on the baseline ECG consisting of a short PR interval and a wide, slurred QRS complex **(delta wave)** owing to early ventricular depolarization of the region adjacent to the pathway. Although the morphology and polarity of the delta wave can suggest the location of the pathway, mapping by intracardiac recordings is required for precise anatomic localization.

Accessory pathways occur in 0.1–0.3% of the population and facilitate reentrant arrhythmias owing to the disparity in refractory periods of the AV node and accessory pathway. **WPW syndrome** refers to a patient with baseline WPW pattern on ECG with associated SVT. Whether the tachycardia is associated with a narrow or wide QRS complex is frequently determined by whether antegrade conduction is through the node (narrow) or the bypass tract (wide). Some bypass tracts only conduct in a retrograde direction. In these cases, the bypass tract is termed "concealed" because it is not readily apparent on a baseline (sinus) ECG. **Orthodromic reentrant tachycardia** accounts for approximately 90% of AVRT episodes and is characterized by conduction antegrade down the AV node and retrograde up the accessory pathway, resulting in a narrow QRS complex (unless an underlying bundle branch block or interventricular conduction delay is present). **Antidromic reentrant tachycardia** conducts antegrade down the accessory pathway and retrograde through the AV node, resulting in a wide and often bizarre-appearing QRS complex that may be mistaken for ventricular tachycardia. Accessory pathways often have shorter refractory periods than specialized conduction tissue and thus tachycardias involving accessory pathways have the potential to be more rapid.

Clinical Findings

Patients with WPW in whom arrhythmia develops often have palpitations, dizziness, or mild chest pain. Most patients that have a delta wave found incidentally on ECG (WPW pattern) do not have a clinical history of arrhythmia and are therefore asymptomatic. However, these patients are still at higher risk for sudden cardiac death than the general population. Atrial fibrillation with antegrade conduction down the accessory pathway and a rapid ventricular response will develop in up to 30% of patients with WPW. If this conduction is very rapid, it can potentially degenerate to ventricular fibrillation. The 10-year risk of sudden cardiac death in patients with WPW syndrome ranges from 0.15% to 0.24%. Risk factors include age younger than 20, a history of symptomatic tachycardia, and multiple accessory pathways.

Multiple risk stratification strategies have been proposed to identify asymptomatic patients with WPW pattern ECG who may be at higher risk for lethal cardiac arrhythmias. A sudden loss of preexcitation during ambulatory monitoring or exercise testing likely indicates an accessory pathway with poor conduction properties and therefore low risk for rapid anterograde conduction. In the absence of this finding, patients may be referred for invasive electrophysiology testing. During the study, patients found to have the shortest preexcited R-R interval during atrial fibrillation of 250 msec or less or inducible SVT are at increased risk for sudden cardiac death and should undergo catheter ablation.

Treatment

A. Pharmacotherapy

Initial treatment of narrow-complex reentrant rhythms involving a bypass tract (orthodromic AVRT) is similar to other forms of PSVT and includes vagal maneuvers, intravenous adenosine, or verapamil. Treatment of wide-complex tachycardia in the presence of an accessory pathway, be it reentrant-type (antidromic AVRT) or atrial fibrillation with antegrade conduction down the bypass tract, must be managed differently. Agents such as calcium channel blockers and beta-blockers may increase the refractoriness of the AV node with minimal or no effect on the accessory pathway, often leading to faster ventricular rates and increasing the risk of ventricular fibrillation. Therefore, these agents should be avoided. Intravenous class Ia (procainamide) and class III (ibutilide) antiarrhythmic agents will increase the refractoriness of the bypass tract and are the medications of choice for wide-complex tachycardias involving accessory pathways. If hemodynamic compromise is present, electrical cardioversion is warranted.

B. Catheter Ablation

For long-term management, catheter ablation is the procedure of choice in patients with accessory pathways and recurrent symptoms or asymptomatic patients with WPW pattern on ECG and high-risk features at baseline or during electrophysiology study. Success rates for ablation of

accessory pathways with radiofrequency catheters exceed 95% in appropriate patients. Major complications from catheter ablation are rare but include AV block, cardiac tamponade, and thromboembolic events. Minor complications, including hematoma at the catheter access site, occur in 1–2% of procedures. For patients not a candidate for catheter ablation, class Ic or class III antiarrhythmic medication may be considered.

When to Refer

- Asymptomatic patients with an incidental finding of WPW pattern on ECG with high-risk features.
- Patients with recurrent or prolonged tachycardia episodes despite treatment with AV nodal blocking agents.
- Patients with preexcitation and a history of atrial fibrillation or syncope.

Al-Khatib SM et al. Risk stratification for arrhythmic events in patients with asymptomatic pre-excitation: a systematic review for the 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia. Circulation. 2016;133:e575. [PMID: 26399661]

ATRIAL FIBRILLATION

ESSENTIALS OF DIAGNOSIS

- Presents as an irregularly irregular heart rhythm on examination and ECG.
- Prevention of stroke should be considered in all patients with risk factors for stroke (those with heart failure, hypertension, age 65 or older, diabetes mellitus, prior history of stroke or TIA, or vascular disease).
- Heart rate control with beta-blocker or calcium channel blockers generally required. Restoration of sinus rhythm with cardioversion, antiarrhythmic medications, or catheter ablation in symptomatic patients.

General Considerations

Atrial fibrillation is the most common chronic arrhythmia, with an incidence and prevalence that rise with age, so that it affects approximately 9% of individuals over age 65 years. It occurs in rheumatic and other forms of valvular heart disease, dilated cardiomyopathy, ASD, hypertension, and CHD as well as in patients with no apparent cardiac disease; it may be the initial presenting sign in thyrotoxicosis, and this condition should be excluded with the initial episode. Atrial fibrillation often appears in a **paroxysmal** fashion before becoming the established rhythm. Pericarditis, chest trauma, thoracic or cardiac surgery, thyroid disorders, obstructive sleep apnea, or pulmonary disease (pneumonia, PE) as well as medications (beta-adrenergic agonists, inotropes, bisphosphonates, and certain chemotherapeutics) may cause attacks in patients with normal hearts. Acute alcohol excess and alcohol withdrawal (termed **holiday heart**) may precipitate atrial fibrillation. For regular, moderate drinkers, abstinence from alcohol reduces recurrences of atrial fibrillation by about 50%.

Atrial fibrillation, particularly when the ventricular rate is uncontrolled, can lead to LV dysfunction, heart failure, or myocardial ischemia (when underlying CAD is present). Perhaps the most serious consequence of atrial fibrillation is the propensity for thrombus formation due to stasis in the atria (particularly the left atrial appendage) and consequent embolization, most devastatingly to the cerebral circulation. ***Untreated, the rate of stroke is approximately 5% per year.*** However, patients with significant obstructive valvular disease, chronic heart failure or LV dysfunction, diabetes mellitus, hypertension, or age over 75 years and those with a history of prior stroke or other embolic events are at substantially higher risk (up to nearly 20% per year in patients with multiple risk factors). A substantial portion of the aging population with hypertension has **asymptomatic** or **"subclinical"** atrial fibrillation, which can be detected with monitoring devices and is also associated with increased risk of stroke, particularly if it lasts for 24 hours or longer. It is not clear whether, and for whom, oral anticoagulation should be used for subclinical atrial fibrillation, a question that is being addressed in ongoing clinical trials.

Clinical Findings

A. Symptoms and Signs

Atrial fibrillation itself is rarely life-threatening; however, it can have serious consequences if the ventricular rate is sufficiently rapid to precipitate hypotension, myocardial ischemia, or tachycardia-induced myocardial dysfunction. Moreover, particularly in patients with risk factors, atrial fibrillation is a major preventable cause of stroke. Although some patients—particularly older or inactive individuals—have relatively few symptoms if the rate is controlled, many patients are aware of the irregular rhythm. Most patients will complain of fatigue whether they experience other symptoms or not. The heart rate may range from quite slow to extremely rapid, but is uniformly irregular unless underlying complete heart block with junctional escape rhythm or a permanent ventricular pacemaker is in place. **Atrial fibrillation is the only common arrhythmia in which the ventricular rate is rapid and the rhythm very irregular.**

B. ECG

The surface ECG typically demonstrates erratic, disorganized atrial activity between discrete QRS complexes occurring in an irregular pattern. The atrial activity may be very fine and difficult to detect on the ECG, or quite coarse and often mistaken for atrial flutter.

C. Echocardiography

Echocardiography provides assessment of chamber volumes, LV size and function, or the presence of concomitant valvular heart disease and should be performed in all

patients with a new diagnosis of atrial fibrillation. TEE is the most sensitive imaging modality to identify thrombi in the left atrium or left atrial appendage prior to any attempt at chemical or electrical cardioversion.

Treatment

A. Newly Diagnosed Atrial Fibrillation

1. Initial management—

A. Hemodynamically unstable patient—If the patient is hemodynamically unstable, usually as a result of a rapid ventricular rate or associated cardiac or noncardiac conditions, hospitalization and immediate treatment of atrial fibrillation are required. Intravenous beta-blockers (esmolol, propranolol, and metoprolol) or calcium channel blockers (diltiazem and verapamil) are usually effective at rate control in the acute setting. Urgent electrical cardioversion is only indicated in patients with shock or severe hypotension, pulmonary edema, or ongoing MI or ischemia. There is a potential risk of thromboembolism in patients undergoing cardioversion who have not received anticoagulation therapy if atrial fibrillation has been *present for more than 48 hours or is of unknown duration*; however, in hemodynamically unstable patients the need for immediate rate control outweighs that risk. An initial shock with 100–200 J is administered in synchrony with the R wave. If sinus rhythm is not restored, an additional attempt with 360 J is indicated. If this fails, cardioversion may be successful after loading with intravenous ibutilide (1 mg over 10 minutes, repeated in 10 minutes if necessary).

B. Hemodynamically stable patient—If the patient has no symptoms, hemodynamic instability, or evidence of important precipitating conditions (such as silent MI or ischemia, decompensated heart failure, PE, or hemodynamically significant valvular disease), hospitalization is usually not necessary. In most of these cases, atrial fibrillation is an unrecognized chronic or paroxysmal condition and should be managed accordingly (see Subsequent Management, below). For new-onset atrial fibrillation, thyroid function tests and echocardiography to assess for occult valvular or myocardial disease should be performed.

In stable patients with atrial fibrillation, a strategy of rate control and anticoagulation is appropriate. This is true whether the conditions that precipitated atrial fibrillation are likely to persist (such as following cardiac or noncardiac surgery, with respiratory failure, or with pericarditis) or might resolve spontaneously over a period of hours to days (such as atrial fibrillation due to excessive alcohol intake or electrolyte imbalance). The choice of agent is guided by the hemodynamic status of the patient, associated conditions, and the urgency of achieving rate control. In the stable patient with atrial fibrillation, a beta-blocker or calcium channel blocker (orally or intravenously) is usually the first-line agent for ventricular rate control. In the setting of MI or ischemia, beta-blockers are the preferred agent. The most frequently used agents are either metoprolol (administered as a 5 mg intravenous bolus, repeated twice at intervals of 5 minutes and then given as needed by repeat boluses or orally at total daily doses of 25–200 mg) or, in unstable patients, esmolol (0.5 mg/kg intravenously, repeated once if necessary, followed by a titrated infusion of 0.05–0.2 mg/kg/minute). If beta-blockers are contraindicated, calcium channel blockers are rapidly effective. Diltiazem (10–20 mg bolus, repeated after 15 minutes if necessary, followed by a maintenance infusion of 5–15 mg/hour) is the preferred calcium blocker if hypotension or LV dysfunction is present. Otherwise, verapamil (5–10 mg intravenously over 2–3 minutes, repeated after 30 minutes if necessary) may be used. Rate control using digoxin is slow (onset of action more than 1 hour with peak effect at 6 hours) and may be inadequate and is rarely indicated for use in the acute setting. Similarly, amiodarone, even when administered intravenously, has a relatively slow onset and is most useful as an adjunct when rate control with the previously cited agents is incomplete or contraindicated or when cardioversion is planned in the near future. Care should be taken in patients with hypotension or heart failure because the rapid intravenous administration of amiodarone may worsen hemodynamics.

Up to two-thirds of patients experiencing acute onset (shorter than 36 hours) of atrial fibrillation will spontaneously revert to sinus rhythm without the need for cardioversion. If atrial fibrillation has been present for more than a week, spontaneous conversion is unlikely and cardioversion may be considered for symptomatic patients. Importantly, **if the onset of atrial fibrillation was more than 48 hours prior to presentation (or unknown), a transesophageal echocardiogram should be performed prior to cardioversion to exclude left atrial thrombus.** If thrombus is present, the cardioversion is delayed until after a 3-week period of therapeutic anticoagulation. In either case, because atrial contractile activity may not recover for several weeks after restoration of sinus rhythm in patients who have been in atrial fibrillation for more than 48 hours, cardioversion should be followed by anticoagulation *for at least 1 month* unless there is a strong contraindication. Younger patients without heart failure, diabetes, hypertension, or other risk factors for stroke may not require long-term anticoagulation.

2. Subsequent management—If immediate cardioversion is not performed, adequate rate control can usually be achieved with beta-blockers or nondihydropyridine calcium channel blockers. Choice of the initial rate control medication is best based on the presence of accompanying conditions: Hypertensive patients can be given beta-blockers or calcium blockers (see Tables 11–9 and 11–7). Patients with CHD or heart failure should receive a beta-blocker preferentially, whereas beta-blockers should be avoided in patients with severe COPD or asthma. Long-term use of digoxin is associated with an *increase* in mortality in patients with chronic atrial fibrillation and is rarely indicated. In symptomatic patients, a resting heart rate of less than 80 beats/minute is targeted. In asymptomatic patients without LV dysfunction, a more lenient resting heart rate of up to 100–110 beats/minute is reasonable. Ambulatory monitoring to assess heart rate during exercise should be considered in all patients with a goal not to exceed maximum predicted heart rate (220 – age).

A. Anticoagulation—For patients with atrial fibrillation, even when it is paroxysmal or occurs rarely, the need for oral anticoagulation should be evaluated and treatment initiated for those without strong contraindication. Patients with **lone atrial fibrillation** (eg, no evidence of associated heart disease, hypertension, atherosclerotic vascular disease, diabetes mellitus, or history of stroke or TIA) under age 65 years need no antithrombotic treatment. Patients with **transient atrial fibrillation**, such as in the setting of acute MI or pneumonia, but no prior history of arrhythmia, are at high risk for future development of atrial fibrillation and appropriate anticoagulation should be initiated based on risk factors. If the cause is reversible, such as after coronary artery bypass surgery or associated with hyperthyroidism, then long-term anticoagulation is not necessary.

In addition to the traditional five risk factors that comprise the **$CHADS_2$ score** (heart failure, hypertension, age 75 years or older, diabetes mellitus, and [2 points for] history of stroke or TIA), the European and American guidelines recommend that three additional factors included in the **CHA_2DS_2-VASc** score be considered: age 65–74 years, female sex, and presence of vascular disease (Table 10–10). *The CHA_2DS_2-VASc score is especially relevant for patients who have a $CHADS_2$ score of 0 or 1;* if the CHA_2DS_2-VASc score is greater than or equal to 2, oral anticoagulation is recommended, and if CHA_2DS_2-VASc score is 1, oral anticoagulation should be considered, taking into account risk, benefit, and patient preferences. Female sex is a relatively weak factor, however, and the European guidelines have removed it from their risk assessment, so that oral anticoagulation is indicated for men who are CHA_2DS_2-VASc of 2 and women who are CHA_2DS_2-VASc of 3. (The use of warfarin is discussed in the section on Selecting Appropriate Anticoagulant Therapy in Chapter 14.) Unfortunately, studies show that *only about half* of patients with atrial fibrillation and an indication for oral anticoagulation are receiving it, and even when treated with warfarin, they are out of the target INR range nearly half the time. *One reason for undertreatment is the misperception that aspirin is useful for prevention of stroke due to atrial fibrillation.* In the European guidelines, aspirin is given a class III A recommendation, indicating that it should *not* be used because of harm (and with no good evidence of benefit). Cardioversion, if planned, should be performed after at least 3–4 weeks of anticoagulation at a therapeutic level (or after exclusion of left atrial appendage thrombus by transesophageal echocardiogram as discussed above). **Anticoagulation clinics** with systematic management of warfarin dosing and adjustment have been shown to result in better maintenance of target anticoagulation.

Four DOACs—dabigatran, rivaroxaban, apixaban, and edoxaban—have been shown to be at least as effective as warfarin for stroke prevention in patients with atrial fibrillation and have been approved by the FDA for this indication (Table 10–11). These medications have *not* been studied in patients with moderate or severe mitral stenosis, and they should *not* be used for patients with mechanical prosthetic valves. The term "nonvalvular atrial fibrillation" is no longer used in the American or European guidelines since most patients with other types of valvular heart disease have been included in trials of DOACs, which are equally effective in these patients.

Dabigatran (studied in the RE-LY trial) is superior to warfarin at preventing stroke at the 150 mg twice daily dose, and it is noninferior at the 110 mg twice daily dose, although this dose is not approved for treatment of atrial

Table 10–10. CHA_2DS_2-VASc Risk Score for assessing risk of stroke and for selecting antithrombotic therapy for patients with atrial fibrillation.

CHA_2DS_2-VASc Risk Score	
Heart failure or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke, transient ischemic attack, or thromboembolism	2
Vascular disease (previous MI, peripheral artery disease, or aortic plaque)	1
Age 65–74 years	1
Female sex (but not a risk factor if female sex is the only factor)	1
Maximum score	9

Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc Score	Patients (n = 7329)	Adjusted stroke rate (%/year)
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7 %
9	14	15.2%

CHA_2DS_2-VASc score = 0: recommend no antithrombotic therapy

CHA_2DS_2-VASc score = 1: recommend antithrombotic therapy with oral anticoagulation or antiplatelet therapy but preferably oral anticoagulation

CHA_2DS_2-VASc score = 2: recommend oral anticoagulation

CHA_2DS_2-VASc, Cardiac failure, Hypertension, Age ≥ 75 years (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female).

Data from Camm AJ et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33(21):2719–2747.

Table 10–11. DOACs for stroke prevention in patients with nonvalvular atrial fibrillation.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Class	Antithrombin	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Bleeding risk compared to warfarin	Less intracranial bleeding Higher incidence of GI bleeding	Less intracranial bleeding Higher incidence of GI bleeding	Substantially lower risk of major bleeding Less intracranial bleeding	Lower risk of major bleeding Less intracranial bleeding
Dosage	110 mg twice daily 150 mg twice daily	20 mg once daily (give with food)	5 mg twice daily	60 mg once daily
Dosage adjustments	75 mg twice daily for creatinine clearance[1] 15–30 mL/minute (approved in the United States but not tested in clinical trials)	15 mg once daily for creatinine clearance[1] < 50 mL/minute	2.5 mg twice daily for patients with at least two of three risk factors: 1. Age ≥ 80 years 2. Body weight ≤ 60 kg 3. Serum creatinine ≥ 1.5 mg/dL	30 mg once daily for creatinine clearance[1] ≤ 50 mL/minute FDA recommends not to use if creatinine clearance[1] > 95 mL/minute

[1]Creatinine clearance calculated by Cockcroft-Gault equation.

Data from Nishimura RA et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(23):e521–643.

fibrillation in the United States. Both doses result in *less* intracranial hemorrhage than warfarin but also in *more* GI bleeding than warfarin. Neither dabigatran nor any of the DOACs should be used in patients with mechanical prosthetic heart valves where the medications are less effective and riskier.

Rivaroxaban is noninferior to warfarin for stroke prevention in atrial fibrillation (in the ROCKET-AF trial). Rivaroxaban is dosed at 20 mg once daily, with a reduced dose (15 mg/day) for patients with creatinine clearances between 15 and 50 mL/minute. It should be administered *with food*, since that results in a 40% higher drug absorption. Similar to dabigatran, there is substantially less intracranial hemorrhage with rivaroxaban than warfarin.

Apixaban is more effective than warfarin at stroke prevention while having a substantially lower risk of major bleeding (in the ARISTOTLE trial) and a lower risk of all-cause mortality. The apixaban dosage is 5 mg twice daily or 2.5 mg twice daily for patients with two of three high-risk criteria (age 80 years or older, body weight 60 kg or less, and serum creatinine of 1.5 mg/dL or more). Apixaban is associated with less intracranial hemorrhage and is well tolerated. Apixaban was also shown to be superior to aspirin (and better tolerated, with comparable rates of bleeding) in the AVERROES trial of patients deemed not suitable for warfarin. Apixaban has been studied in a small trial of patients receiving hemodialysis, in which the plasma concentrations were in an acceptable range using standard dosing criteria.

Edoxaban, 60 mg once a day, is noninferior to warfarin for stroke prevention with lower rates of major bleeding and lower rates of hemorrhagic stroke (studied in the ENGAGE-AF trial). Edoxaban carries a boxed warning in FDA labelleling that it should *not* be used in patients whose creatinine clearance is more than 95 mL/minute because it is less effective in this population. The dose is decreased to 30 mg/day for patients whose creatinine clearance is less than or equal to 50 mL/minute.

These four DOACs have important advantages over warfarin, and therefore, they are recommended preferentially over VKAs. In practice, these medications are often underdosed. They should be used at the doses shown to be effective in the clinical trials as shown in Table 10–11. Even though labeled for "nonvalvular" atrial fibrillation, the DOACs are safe and effective for patients with moderate or severe valvular abnormalities, with the exception of moderate or severe mitral stenosis. In part because of lower rates of intracerebral hemorrhage, *DOACs have particular advantage over warfarin in the elderly and the frail,* including patients with history of falls. For patients who fall, oral anticoagulation should generally be used, except for patients who are suffering head trauma with falls.

There are some patients with atrial fibrillation, however, who *should* be treated with VKAs. These patients include those who have mechanical prosthetic valves, advanced kidney disease (creatinine clearance less than 25 mL/minute), or moderate or severe mitral stenosis, and those who cannot afford the newer medications. Apixaban may be a reasonable option for patients with creatinine clearance less than 25 mL/minute, with one small randomized trial of patients receiving hemodialysis suggesting that it may be reasonable. Patients who have been stable while receiving warfarin for a long time, with a high time in target INR range, and who are at lower risk for intracranial hemorrhage will have relatively less benefit with a switch to a newer medication. It is important to note, however, that most patients who have intracranial hemorrhage while taking warfarin have had a recent INR below 3.0, so that good INR control does not ensure avoidance of intracranial bleeding. One way to reduce bleeding for patients taking oral anticoagulants is to avoid concurrent aspirin, unless the patient has a clear indication, like recent MI or

coronary stent. Even then, use of oral anticoagulant plus clopidogrel without aspirin, or with only a brief period of "triple" therapy and then discontinuation of aspirin, may be a reasonable approach, as has been shown in clinical trials comparing rivaroxaban and dabigatran with warfarin.

There are some important practical issues with using the DOACs. It is important to monitor kidney function at baseline and at least once a year, or more often for those with impaired kidney function. Each of the medications interacts with other medications affecting the P-glycoprotein pathway, like oral ketoconazole, verapamil, dronederone, and phenytoin. To transition patients from warfarin to a DOAC, wait until the INR decreases to about 2.0. Each of the medications has a half-life of about 10–12 hours for patients with normal kidney function. For elective procedures, stop the medications two to three half-lives (usually 24–48 hours) before procedures with low to moderate bleeding risk (ie, colonoscopy, dental extraction, cardiac catheterization), and five half-lives before procedures like major surgery. Discontinuation times should be extended in patients with impaired renal function, particularly with dabigatran. There are no practical tests to immediately measure the effect of the medications, although a normal aPTT suggests little effect with dabigatran, and a normal prothrombin suggests little effect with rivaroxaban. For rivaroxaban and apixaban, chromogenic Xa assays will measure the effect, but may not be readily available. For bleeding, standard measures (eg, diagnosing and controlling the source, stopping antithrombotic agents, and replacing blood products) should be taken. If the direct-acting medication was taken in the prior 2–4 hours, use activated oral charcoal to reduce absorption. If the patient is taking aspirin, consider platelet transfusion. Antidotes should be considered for life-threatening bleeding or for patients with need for immediate surgery, or both. For cardioversion, the DOACs appear to have similar rates of subsequent stroke as warfarin, as long as patients have been taking the medications and adherent for at least several weeks. Like with warfarin, there appears to be a 1.5- to 2-fold increased rate of bleeding associated with the use of aspirin in combination with the DOACs. Even patients with atrial fibrillation and stable coronary disease taking a DOAC at least 1 year from most recent coronary stent or coronary bypass surgery appear to have substantially greater risk than benefit from the use of aspirin. Therefore, **aspirin should *not* be used with the DOACs unless there is a clear indication, such as coronary stents or acute coronary syndrome within the prior year.**

A patient with severe bleeding while taking dabigatran may be treated with the reversal agent **idarucizumab,** which is a humanized monoclonal antibody approved by the FDA for rapid reversal of the anticoagulation effects, for use in the event of severe bleeding or the need for an urgent procedure. This treatment is widely available in the United States. **Andexanet alfa**, an intravenous factor Xa decoy, is approved for reversal of factor Xa inhibitors. Four-factor prothrombin complex concentrate may partially reverse the effects of these agents. Due to the short half-life of the DOACs (10–12 hours with normal kidney function), supportive measures (local control, packed RBCs, platelets) may suffice until the medication has cleared.

Each of the DOACs appears to be safe and effective around the time of electrical cardioversion. In each of these trials, and in one modest-sized prospective randomized trial of rivaroxaban that specifically addressed cardioversion, the rates of stroke were low (and similar to warfarin) with the DOACs when given for at least 3–4 weeks prior to cardioversion. An advantage of the DOACs is that when stable anticoagulation is desired before elective cardioversion, it is achieved faster than with warfarin.

In patients who are unsuitable for long-term anticoagulation due to excessive bleeding risk, left atrial appendage occluders (including the Watchman and Amulet devices) have been shown to protect against stroke, although they are not as effective as warfarin in preventing ischemic stroke. Occlusion of the left atrial appendage during cardiac surgery provides further protection against ischemic stroke over and above ongoing oral anticoagulant use.

B. Rate control or rhythm control—After assessing stroke risk and initiating anticoagulation where appropriate, two main treatment strategies for long-term management of atrial fibrillation exist: rate control or rhythm control, although they are not mutually exclusive. Rate control should be considered background treatment in nearly all patients with atrial fibrillation, regardless of whether rhythm restoration is eventually pursued, and may be considered the primary treatment in patients with minimal to no symptoms related to long-standing atrial fibrillation. In patients with recent-onset atrial fibrillation (less than 1 year), the EAST-AFNET 4 trial found that rhythm control with antiarrhythmic medication or catheter ablation is associated with a lower risk of death from cardiovascular causes, stroke, or hospitalization for heart failure.

The decision to pursue rhythm control is often individualized, based on symptoms, the type of atrial fibrillation (paroxysmal or persistent), comorbidities (such as heart failure), as well as general health status. As first treatment, elective cardioversion following an appropriate period of anticoagulation (minimum of 3 weeks) or exclusion of left atrial thrombus by TEE is generally recommended in patients in whom atrial fibrillation is thought to be of recent onset or when there is an identifiable precipitating factor. Similarly, cardioversion is appropriate in patients who remain symptomatic from the rhythm despite efforts to achieve rate control.

In cases in which elective cardioversion is required, it may be accomplished pharmacologically or electrically. Pharmacologic cardioversion with intravenous **ibutilide** (1 mg over 10 minutes, repeated in 10 minutes if necessary) or **procainamide** (15 mg/kg over 30 minutes) may be used in a setting in which the patient can undergo continuous ECG monitoring for at least 4–6 hours following administration. Pretreatment with intravenous magnesium (1–2 g) may prevent rare episodes of torsades de pointes associated with ibutilide administration. In patients in whom a decision has been made to continue antiarrhythmic therapy to maintain sinus rhythm (see next paragraph), cardioversion can be attempted with an agent that is being considered for

long-term use. For instance, after therapeutic anticoagulation has been established, **amiodarone** can be initiated on an outpatient basis (400 mg twice daily for 2 weeks, followed by 200 mg twice daily for at least 2–4 weeks and then a maintenance dose of 200 mg daily). Because amiodarone increases the prothrombin time in patients taking warfarin and increases digoxin levels, careful monitoring of anticoagulation and medication levels is required.

Other antiarrhythmic medications that can be used for long-term maintenance therapy include propafenone, flecainide, dronedarone, dofetilide, and sotalol. **Dofetilide** (125–500 mcg twice daily orally) must be initiated in hospital due to the potential risk of torsades de pointes and the downward dose adjustment that is required for patients with renal impairment. **Propafenone** (150–300 mg orally every 8 hours) and **flecainide** (50–150 mg orally twice daily) should be avoided in patients with structural heart disease (CAD, systolic dysfunction, or significant LVH) and should be used in conjunction with an AV nodal blocking medication, especially if there is a history of atrial flutter. **Sotalol** (80–160 mg orally twice daily) should be initiated in the hospital in patients with structural heart disease due to a risk of torsades de pointes; it is not very effective for converting atrial fibrillation but can be used to maintain sinus rhythm following cardioversion. **Dronedarone** should not be used in patients with recent decompensated heart failure or when atrial fibrillation has become persistent.

In patients treated long-term with an antiarrhythmic agent, sinus rhythm will persist in 30–50%. Given this high rate of arrhythmia recurrence, the decision to maintain long-term anticoagulation should be based on risk factors (CHA_2DS_2-VASc score, Table 10–10) and not on the perceived presence or absence of atrial fibrillation, since future episodes may be asymptomatic.

B. Recurrent and Refractory Atrial Fibrillation

1. Recurrent paroxysmal atrial fibrillation—For select patients with symptomatic but rare (a few times a year) episodes of atrial fibrillation, an effective treatment strategy is on-demand pharmacologic cardioversion, termed **pill-in-the-pocket treatment**. Patients without coronary or structural heart disease may be given flecainide (200–300 mg) or propafenone (450–600 mg) in addition to a beta-blocker or nondihydropyridine calcium channel blocker as a single dose at the onset of symptoms. It is recommended that the first such treatment take place in a monitored setting (eg, the emergency department or hospital) to evaluate safety and effectiveness. For more frequent, symptomatic arrhythmic episodes, daily antiarrhythmic agents are first-line therapy; however, they are not often successful in preventing all paroxysmal atrial fibrillation episodes and long-term tolerability is poor.

2. Refractory atrial fibrillation—Atrial fibrillation should be considered refractory if it causes persistent symptoms or limits activity despite attempts at rate or rhythm control. If antiarrhythmic or rate control medications fail to improve symptoms, catheter ablation around the pulmonary veins to isolate the triggers that initiate and maintain atrial fibrillation may be considered. It is a reasonable therapy for individuals with symptomatic paroxysmal or persistent atrial fibrillation that is refractory to pharmacologic therapy and for select patients (younger than 65 years or with concurrent heart failure) as first-line therapy. The primary benefit of catheter ablation is an improvement in quality of life. In the CABANA trial, there was no difference in the primary endpoint of death, disabling stroke, serious bleeding, or cardiac arrest in patients randomized to catheter ablation versus medical therapy as first treatment for symptomatic atrial fibrillation. Ablation is successful about 50–70% of the time but repeat ablation may be required in up to 20% of patients. The procedure is routinely performed in the electrophysiology laboratory using a catheter-based approach and adverse event rates are low when performed by experienced operators. Surgical ablation can also be performed via a subxiphoid approach thoracoscopically, via thoracotomy, or via median sternotomy in the operating room as a stand-alone or adjunct procedure. Finally, in symptomatic patients with poor rate control and deemed inappropriate for pulmonary vein isolation, radiofrequency ablation of the AV node and permanent pacing ensure rate control and may facilitate a more physiologic rate response to activity, but this is usually performed only after other therapies have failed.

When to Refer

- Symptomatic atrial fibrillation with or without adequate rate control.
- Asymptomatic atrial fibrillation with poor rate control despite AV nodal blockers.
- Patients at risk for stroke who have not tolerated oral anticoagulants.

Kirchhof P et al; EAST-AFNET 4 Trial Investigators. Early rhythm-control therapy in patients with atrial fibrillation. N Engl J Med. 2020;383:1305. [PMID: 32865375]

Packer DL et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. JAMA. 2019;321:1261. [PMID: 30874766]

Whitlock RP et al. Left atrial appendage occlusion during cardiac surgery to prevent stroke. N Engl J Med. 2021;384:2081. [PMID: 33999547]

ATRIAL FLUTTER

ESSENTIALS OF DIAGNOSIS

- Rapid, regular tachycardia presenting classically with 2 to 1 block in the AV node and ventricular heart rate of 150 beats/minute. ECG shows "sawtooth" pattern of atrial activity (rate 300 beats/minute).
- Stroke risk should be considered equivalent to that with atrial fibrillation.
- Catheter ablation is highly successful and is considered the definitive treatment for typical atrial flutter.

General Considerations

Atrial flutter is less common than fibrillation. It may occur in patients with structurally normal hearts but is more commonly seen in patients with COPD, valvular or structural heart disease, ASD, or surgically repaired congenital heart disease.

Clinical Findings

Patients typically present with complaints of palpitations, fatigue, or mild dizziness. In situations where the arrhythmia is unrecognized for a prolonged period of time, patients may present with symptoms and signs of heart failure (dyspnea, exertional intolerance, edema) due to tachycardia-induced cardiomyopathy. The ECG typically demonstrates a **"sawtooth"** pattern of atrial activity in the inferior leads (II, III, and AVF). The reentrant circuit generates atrial rates of 250–350 beats/minute, usually with transmission of every second, third, or fourth impulse through the AV node to the ventricles.

Treatment

Ventricular rate control is accomplished using the same agents used in atrial fibrillation, but it is generally more difficult. Conversion of atrial flutter to sinus rhythm with class I antiarrhythmic agents is also difficult to achieve, and administration of these medications has been associated with slowing of the atrial flutter rate to the point at which 1:1 AV conduction can occur at rates in excess of 200 beats/minute, with subsequent hemodynamic collapse. The intravenous class III antiarrhythmic agent ibutilide has been significantly more successful in converting atrial flutter (see Table 10–9). About 50–70% of patients return to sinus rhythm within 60–90 minutes following the infusion of 1–2 mg of this agent. Electrical cardioversion is also very effective for atrial flutter, with approximately 90% of patients converting following synchronized shocks of as little as 25–50 J.

Although the organization of atrial contractile function in this arrhythmia may provide some protection against thrombus formation, **the risk of thromboembolism should be considered equivalent to that with atrial fibrillation** due to the common coexistence of these arrhythmias. Precardioversion anticoagulation is not necessary for atrial flutter of less than 48 hours duration except in the setting of mitral valve disease. As with atrial fibrillation, anticoagulation should be continued for at least 4 weeks after electrical or chemical cardioversion and chronically in patients with risk factors for thromboembolism.

Catheter ablation is the treatment of choice for long-term management of atrial flutter owing to the high success rate and safety of the procedure. The anatomy of the typical circuit is well defined and catheter ablation within the right atrium results in immediate and permanent elimination of atrial flutter in more than 90% of patients. Due to the frequent coexistence of atrial flutter with atrial fibrillation, however, some patients may require catheter ablation of both arrhythmias. If pharmacologic therapy is chosen, class III antiarrhythmics (amiodarone or dofetilide) are generally preferred (see Table 10–9).

When to Refer

All patients with atrial flutter should be referred to a cardiologist or cardiac electrophysiologist for consideration of definitive treatment with catheter ablation.

ATRIAL TACHYCARDIA

ESSENTIALS OF DIAGNOSIS

- Characterized by bursts of rapid, regular tachycardia.
- Multifocal atrial tachycardia commonly seen with severe COPD and presents with three or more distinct P wave morphologies on ECG, often confused for atrial fibrillation. Treatment of the underlying lung disease is most effective therapy.

General Considerations

Atrial tachycardia is an uncommon form of SVT characterized by paroxysms or bursts of rapid, regular arrhythmia due to focal atrial impulses originating outside of the normal sinus node. Common sites include the tricuspid annulus, the crista terminalis of the right atrium and the coronary sinus. **Multifocal atrial tachycardia** is a particular subtype seen in patients with severe COPD and characterized by varying P wave morphology (by definition, three or more foci) and markedly irregular PP intervals. The rate is usually between 100 beats/minute and 140 beats/minute, and it is often confused for atrial fibrillation. **Solitary atrial premature beats** are benign and generally not associated with underlying cardiac disease. They occur when an ectopic focus in the atria fires before the next sinus node impulse. The contour of the P wave usually differs from the patient's normal complex, unless the ectopic focus is near the sinus node. Acceleration of the heart rate by any means usually abolishes most premature beats.

Clinical Findings

Focal atrial tachycardias are usually intermittent and self-limiting although incessant forms do exist and may present with signs and symptoms of heart failure due to tachycardia-induced cardiomyopathy. Most patients report palpitations with an abrupt onset, similar to other forms of PSVT. Patients with underlying cardiac pathology (eg, CHD) can present with dyspnea or angina. Close inspection of the P wave on 12-lead ECG suggests a focus away from the sinus node, although certain locations (eg, high right atrial crista terminalis) may mimic sinus tachycardia. In this situation, the abrupt onset and offset of the arrhythmia is helpful in distinguishing atrial from sinus tachycardia, although electrophysiologic study is sometimes necessary.

Treatment

Initial management of atrial tachycardia is similar to other types of PSVT; however, vagal maneuvers and intravenous

adenosine are generally less effective. Intravenous beta-blockers or calcium channel blockers can be given in the hemodynamically stable patient with a transition to oral formulations for long-term management. Antiarrhythmic medications or catheter ablation should be considered in patients who continue to have symptomatic episodes. Long-term anticoagulation is not indicated in the absence of coexistent atrial fibrillation or atrial flutter.

For patients with multifocal atrial tachycardia, treatment of the underlying condition (eg, COPD) is paramount; verapamil, 240–480 mg orally daily in divided doses, may be effective in some patients.

When to Refer

All patients with atrial tachycardia in whom initial medical management fails should be referred to a cardiologist or cardiac electrophysiologist.

VENTRICULAR PREMATURE BEATS (Ventricular Extrasystoles)

ESSENTIALS OF DIAGNOSIS

- Common but rarely symptomatic.
- Ambulatory ECG monitoring to quantify daily burden of PVCs. Asymptomatic patients with > 10% PVC burden should have periodic echocardiogram to exclude development of LV dysfunction.

General Considerations

Ventricular premature beats, or **PVCs,** are isolated beats typically originating from the outflow tract or His-Purkinje regions of ventricular tissue. In most patients, the presence of PVCs is a benign finding; however, they rarely may trigger ventricular tachycardia or ventricular fibrillation, especially in patients with underlying heart disease.

Clinical Findings

Patients may be asymptomatic or experience palpitations, dizziness, or vague chest pain. Some patients feel the irregular beat; however, symptoms can often be secondary to post-PVC augmentation of contractility or a post-PVC compensatory pause. Exercise generally abolishes premature beats in normal hearts, and the rhythm becomes regular. PVCs are characterized by wide QRS complexes that differ in morphology from the patient's normal beats. They are usually not preceded by a P wave, although retrograde ventriculoatrial conduction may occur. **Bigeminy** and **trigeminy** are arrhythmias in which every second or third beat is premature. Ambulatory ECG monitoring may reveal more frequent and complex PVCs than occur in a single routine ECG. An increased frequency of PVCs during exercise is associated with a higher risk of cardiovascular mortality and should be investigated further.

Treatment

If no associated cardiac disease is present and if the ectopic beats are asymptomatic, no therapy is indicated. Mild symptoms or anxiety from palpitations may be allayed with reassurance to the patient of the benign nature of this arrhythmia. If PVCs are frequent (bigeminal or trigeminal pattern) or multifocal, electrolyte abnormalities (ie, hypo- or hyperkalemia and hypomagnesemia) and occult cardiac disease (ie, ischemic heart disease or LV dysfunction) should be excluded. In addition, an echocardiogram should be performed in patients in whom a burden of PVCs of greater than 10,000 per day has been documented by ambulatory ECG monitoring. Pharmacologic treatment is indicated only for patients who are symptomatic or who develop cardiomyopathy thought to be due to a high burden of PVCs (generally greater than 10% of daily heart beats). Beta-blockers or nondihydropyridine calcium channel blockers are appropriate as first-line therapy. The class I and III antiarrhythmic agents (see Table 10–9) may be effective in reducing PVCs but are often poorly tolerated and can be proarrhythmic in up to 5% of patients. Catheter ablation is a well-established therapy for symptomatic individuals who do not respond to medication or for those patients whose burden of ectopic beats has resulted in a cardiomyopathy.

When to Refer

Patients with symptomatic PVCs who do not respond to initial medical management or asymptomatic patients with daily PVC burden greater than 10% on ambulatory ECG monitoring should be referred to a cardiologist or cardiac electrophysiologist.

VENTRICULAR TACHYCARDIA

ESSENTIALS OF DIAGNOSIS

- Fast, wide QRS complex on ECG.
- Associated with ischemic heart disease, particularly in older patients.
- In the absence of reversible cause, implantable cardioverter defibrillator (ICD) is recommended if meaningful life expectancy is > 1 year.

General Considerations

Ventricular tachycardia is defined as three or more consecutive ventricular premature beats. It is classified as either **nonsustained** (lasting less than 30 seconds and terminating spontaneously) or **sustained** with a heart rate greater than 100 beats/minute. In individuals without heart disease, nonsustained ventricular tachycardia is generally associated with a benign prognosis. In patients with structural heart disease, nonsustained ventricular tachycardia is associated with an increased risk of subsequent symptomatic ventricular tachycardia and sudden death, especially when seen more than 48 hours after MI.

Ventricular tachycardia is a frequent complication of acute MI and dilated cardiomyopathy but may occur in chronic coronary disease, HCM, myocarditis, and in most other forms of myocardial disease. It can also be a consequence of atypical forms of cardiomyopathies, such as arrhythmogenic RV cardiomyopathy. However, idiopathic ventricular tachycardia can also occur in patients with structurally normal hearts. **Accelerated idioventricular rhythm** is a regular wide complex rhythm with a rate of 60–120 beats/minute, usually with a gradual onset. It occurs commonly in acute infarction and following reperfusion with thrombolytic medications. Treatment is not indicated unless there is hemodynamic compromise or more serious arrhythmias. **Torsades de pointes,** a form of ventricular tachycardia in which QRS morphology twists around the baseline, may occur in the setting of severe hypokalemia, hypomagnesemia, or after administration of a medication that prolongs the QT interval.

Clinical Findings

A. Symptoms and Signs

Patients commonly experience palpitations, dyspnea, or lightheadedness, but on rare occasion may be asymptomatic. Syncope or cardiac arrest can be presenting symptoms in patients with underlying cardiac disease or other severe comorbidities. Episodes may be triggered by exercise or emotional stress.

B. Diagnostic Studies

Comprehensive blood laboratory work should be performed because ventricular tachycardia can occur in the setting of hypokalemia and hypomagnesemia. Cardiac markers may be elevated when ventricular tachycardia presents in the setting of acute MI or as a consequence of underlying CAD and demand ischemia. In patients with sustained, hemodynamically tolerated ventricular tachycardia, a 12-lead ECG during tachycardia should be obtained. Cardiac evaluation with echocardiography or cardiac MRI, ambulatory ECG monitoring, and exercise testing may be warranted depending on the clinical situation. Survivors of cardiac arrest or life-threatening ventricular arrhythmia should be evaluated for ischemic heart disease (CT or invasive coronary angiography) and undergo revascularization when appropriate.

There is generally no role for invasive electrophysiologic study in patients with sustained ventricular tachycardia who otherwise meet criteria for ICD. In patients with structural heart disease and syncope of unknown cause, or in situations in which the mechanism of wide-complex tachycardia is uncertain, electrophysiologic study may provide important information.

C. Differentiation of Aberrantly Conducted Supraventricular Beats From Ventricular Beats

The distinction on 12-lead ECG of ventricular tachycardia from SVT with aberrant conduction may be difficult in patients with a wide-complex tachycardia; it is important because of the differing prognostic and therapeutic implications of each type. Findings favoring a **ventricular origin** include: (1) AV dissociation; (2) a QRS duration exceeding 0.14 second; (3) capture or fusion beats (infrequent); (4) left axis deviation with right bundle branch block morphology; (5) monophasic (R) or biphasic (qR, QR, or RS) complexes in V_1; and (6) a qR or QS complex in V_6. **Supraventricular origin** is favored by: (1) a triphasic QRS complex, especially if there was initial negativity in leads I and V_6; (2) ventricular rates exceeding 170 beats/minute; (3) QRS duration longer than 0.12 second but not longer than 0.14 second; and (4) the presence of preexcitation syndrome. Patients with a wide-complex tachycardia, especially those with known cardiac disease, should be presumed to have ventricular tachycardia if the diagnosis is unclear.

Treatment

A. Initial Management

The treatment of acute ventricular tachycardia is determined by the degree of hemodynamic compromise and the duration of the arrhythmia. In patients with structurally normal hearts, the prognosis is generally benign and syncope is uncommon. The etiology is often triggered activity from the right or LV outflow tract and immediate treatment with a short-acting intravenous beta-blocker or verapamil may terminate the episode.

In the presence of known or suspected structural heart disease, assessment of hemodynamic stability determines the need for urgent direct current cardioversion. When ventricular tachycardia causes hypotension, heart failure, or myocardial ischemia, immediate synchronized direct current cardioversion with 100–360 J should be performed. If ventricular tachycardia recurs, intravenous amiodarone (150-mg bolus followed by 1 mg/minute infusion for 6 hours and then 0.5 mg/minute for 18 hours) should be administered to achieve a stable rhythm with further attempts at cardioversion as necessary. Significant hypotension can occur with rapid infusions of amiodarone. The management of ventricular tachycardia in the setting of acute MI is discussed in the Complications section of Acute Myocardial Infarction with ST-Segment Elevation.

In patients with sustained ventricular tachycardia who are hemodynamically stable, medical treatment with intravenous amiodarone, lidocaine, or procainamide can be used; however, direct current cardioversion should be performed if the ventricular tachycardia fails to terminate or symptoms worsen. Empiric magnesium replacement (1–2 g intravenously) may help, especially for polymorphic ventricular tachycardia. If polymorphic ventricular tachycardia recurs, increasing the heart rate with isoproterenol infusion (up to 20 mcg/minute) or atrial pacing with a temporary pacemaker (at 90–120 beats/minute) will effectively shorten the QT interval to prevent further episodes. In patients with polymorphic ventricular tachycardia in the setting of a normal QT interval, myocardial ischemia should be considered with prompt evaluation and coronary revascularization performed as indicated.

B. Long-Term Management

Patients with symptomatic or sustained ventricular tachycardia in the absence of a reversible precipitating cause

(acute MI or ischemia, electrolyte imbalance, medication toxicity, etc) are at high risk for recurrence. In patients with structurally normal hearts and ventricular tachycardia with typical outflow tract (left bundle branch block with inferior axis) or left posterior fascicle (right bundle branch block with superior axis) appearance on ECG, suppressive treatment with beta-blocker or a nondihydropyridine calcium channel blocker may be tried. Catheter ablation has a high success rate in these patients who fail initial medical treatment. In patients with significant LV dysfunction, subsequent sudden death is common and ICD implantation is recommended if meaningful survival is expected to be longer than 1 year. Beta-blockers are the mainstay for medical treatment of ventricular tachycardia in patients with structural heart disease. Antiarrhythmic medications have not been shown to lower mortality in these patients, but may decrease subsequent episodes and reduce the number of ICD shocks. Amiodarone is generally preferred in patients with structural heart disease but sotalol may be considered as well. Catheter ablation is an important treatment option for those patients with recurrent tachycardia who do not respond to or are intolerant of medical therapy; however, recurrence rates are high.

When to Refer

Any patient with sustained ventricular tachycardia or syncope of unknown cause in the presence of underlying structural cardiac disease.

Al-Khatib SM et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2018;72:e91. [PMID: 29097296]

VENTRICULAR FIBRILLATION & SUDDEN DEATH

ESSENTIALS OF DIAGNOSIS

- Most patients with sudden cardiac death have underlying CHD.
- In the absence of reversible cause, ICD is recommended.

General Considerations

Sudden cardiac death is defined as unexpected nontraumatic death in clinically well or stable patients who die within 1 hour after onset of symptoms. The causative rhythm in most cases is ventricular fibrillation. **Sudden cardiac arrest** is a term reserved for the successful resuscitation of ventricular fibrillation, either spontaneously or via intervention (defibrillation).

Clinical Findings

Approximately 70% of cases of sudden cardiac death are attributable to underlying CHD; in up to 40% of patients, sudden cardiac death may be the initial manifestation of CHD. In patients younger than 35, most sudden cardiac death (SCD) is caused by inherited heart disease (long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, HCM, arrhythmogenic RV cardiomyopathy, dilated cardiomyopathy). Over the age of 35, CHD is the most common cause of SCD, although inherited causes are common up until the age of 50. Noninherited forms of heart disease can also lead to SCD, including valvular heart disease (aortic stenosis, pulmonic stenosis), congenital heart disease, and myocarditis. Prompt evaluation to exclude reversible causes of sudden cardiac arrest should begin immediately following resuscitation. Laboratory testing should be performed to exclude severe electrolyte abnormalities (particularly hypokalemia and hypomagnesemia) and acidosis and to evaluate cardiac biomarkers. Caution should be taken in attributing cardiac arrest solely to an electrolyte disturbance, however, because laboratory abnormalities may be secondary to resuscitation and not causative of the event. A 12-lead ECG should be performed to evaluate for ongoing ischemia or conduction system disease. Ventricular function should be evaluated with echocardiography. Evaluation for ischemic heart disease (CT or coronary angiography) should be performed to exclude coronary disease as the underlying cause, since revascularization may prevent recurrence. In the absence of coronary disease, contrast-enhanced cardiac MRI may be used to evaluate for the presence of myocardial scar, which is a strong predictor of recurrent ventricular tachycardia/ventricular fibrillation in patients with nonischemic cardiomyopathy.

Treatment

Unless ventricular fibrillation occurs shortly after MI, is associated with ischemia, or is seen with a correctable process (such as an electrolyte abnormality or medication toxicity), surviving patients require intervention since recurrences are frequent. Survivors of cardiac arrest appear to have improved long-term outcomes if a **targeted temperature management protocol** is rapidly initiated and continued for 24–36 hours after cardiac arrest.

Patients who survive sudden cardiac arrest have a high incidence of recurrence, so an **ICD** is generally indicated. Sudden cardiac arrest in the setting of acute ischemia or infarct should be managed with prompt coronary revascularization. However, implantation of a prophylactic ICD in patients immediately after MI is associated with a trend toward *worse* outcomes. These patients may be managed with a **wearable cardioverter defibrillator** until recovery of ventricular function can be assessed by echocardiogram at a later date (6–12 weeks following MI or coronary intervention). In patients in whom ventricular function remains low (EF less than or equal to 35%), a permanent subcutaneous ICD (when pacing is not required) or transvenous ICD should be implanted.

When to Refer

All survivors of sudden cardiac arrest should be referred to a cardiologist or cardiac electrophysiologist.

INHERITED ARRHYTHMIA SYNDROMES

ESSENTIALS OF DIAGNOSIS

- Includes long QT syndrome, Brugada syndrome, arrhythmogenic RV cardiomyopathy, and catecholaminergic polymorphic ventricular tachycardia.
- Genetic testing for patients with suspected congenital long QT syndrome based on family history, ECG or exercise testing, or severely prolonged QT interval (> 500 msec) on serial ECGs.
- Patients with long QT syndrome or catecholaminergic polymorphic ventricular tachycardia should be treated long term with an oral beta-blocker (nadolol or propranolol). ICD is indicated for patients with ventricular arrhythmia or syncope despite medical treatment.

General Considerations

Inherited arrhythmia syndromes may result in life-threatening ventricular arrhythmias due to gene mutations in cardiac channels resulting in abnormal electrolyte regulation across the cardiac cell membrane. **Congenital long QT syndrome** is an uncommon disease (1 in 2500 live births) that is characterized by a long QT interval (usually greater than 470 msec) and ventricular arrhythmia, typically polymorphic ventricular tachycardia. **Acquired long QT syndrome** is usually secondary to use of antiarrhythmic agents (sotalol, dofetilide), methadone, antidepressant medications, or certain antibiotics; electrolyte abnormalities; myocardial ischemia; or significant bradycardia. **Brugada syndrome** accounts for up to 20% of sudden cardiac death in the absence of structural heart disease and is most often due to a defect in a sodium channel gene. **Arrhythmogenic RV cardiomyopathy** is an inherited cardiomyopathy that predominantly affects the right ventricle and is characterized by areas of myocardial replacement with fibrosis and adipose tissue that frequently causes ventricular arrhythmia. **Catecholaminergic polymorphic ventricular tachycardia** is a rare but important cause of sudden cardiac death associated with exercise.

Clinical Findings

Patients with an inherited arrhythmia syndrome have a variable clinical presentation; they may be asymptomatic or have palpitations, sustained tachyarrhythmia, syncope, or sudden cardiac arrest. In young patients, syncopal episodes may be misdiagnosed as a primary seizure disorder. Personal and family history should be thoroughly reviewed in all patients. A 12-lead ECG should be performed with careful attention to any abnormality in the ST segment, T wave, and QT interval. A corrected QT interval longer than 500 msec on serial ECGs in the absence of a secondary cause (medication or electrolyte abnormality) identifies a high-risk subset of patients with long QT syndrome. Ambulatory ECG monitoring may be used to evaluate for ventricular arrhythmias as well as dynamic changes to the QT interval or T wave. Exercise ECG testing may be performed in patients with suspected long QT syndrome to assess for lack of appropriate QT interval shortening with higher heart rates. In cases where the cause of sudden cardiac arrest is suspected to be heritable, genetic testing under the guidance of a multidisciplinary genetics team is recommended to both determine the diagnosis and to facilitate the identification of first-degree family members at risk for developing the same disease.

Treatment

The management of acute polymorphic ventricular tachycardia (torsades de pointes) differs from that of other forms of ventricular tachycardia. Class Ia, Ic, or III antiarrhythmics, which prolong the QT interval, should be avoided—or withdrawn immediately if being used in patients with long QT syndrome. Intravenous beta-blockers may be effective in treating electrical storm due to long QT syndrome or catecholaminergic polymorphic ventricular tachycardia. Increasing the heart rate, whether by infusion of beta-agonist (dopamine or isoproterenol) or temporary atrial or ventricular pacing, is an effective approach that can both break and prevent the rhythm.

Long-term treatment of patients with inherited arrhythmia syndromes depends on the presence of high-risk features. Use of beta-blockers (particularly propranolol or nadolol) is the mainstay of treatment for patients with long QT syndrome or catecholaminergic polymorphic ventricular tachycardia. Surgical cervicothoracic sympathectomy should be considered for patients who do not respond to or are intolerant of beta-blockers. There is no reliable medication therapy for Brugada syndrome and prevention of arrhythmias focuses on prompt treatment of exacerbating triggers, particularly fever. Antiarrhythmic medications should be avoided in patients with inherited arrhythmia syndromes except for specific identified genetic abnormalities under the direction of a specialist. ICD implantation is generally recommended for patients with an inherited arrhythmia syndrome in whom sudden cardiac arrest is the initial presentation. An ICD should be considered in patients with recurrent sustained ventricular arrhythmias or syncope despite medical therapy.

When to Refer

Any patient with known or suspected inherited arrhythmia syndrome or with severe corrected QT interval prolongation (greater than 500 msec on serial ECGs) should be referred to a cardiologist or cardiac electrophysiologist.

Stiles MK et al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. Heart Rhythm. 2021;18:e1. [PMID: 33091602]

SYNCOPE

ESSENTIALS OF DIAGNOSIS

- Transient loss of consciousness and postural tone from vasodepressor or cardiogenic causes with prompt recovery without resuscitative measures.
- High-risk features include history of structural heart disease, abnormal ECG, and age > 60 years.

General Considerations

Syncope is a symptom defined as a transient, self-limited loss of consciousness, usually leading to a fall. Thirty percent of the adult population will experience at least one episode of syncope. It accounts for approximately 3% of emergency department visits. A specific cause of syncope is identified in about 50% of cases during the initial evaluation. The prognosis is relatively favorable except when accompanying cardiac disease is present. In many patients with recurrent syncope or near syncope, arrhythmias are not the cause. This is particularly true when the patient has no evidence of associated heart disease by history, examination, standard ECG, or noninvasive testing. The history is the most important component of the evaluation to identify the cause of syncope.

Reflex (neurally mediated) syncope may be due to excessive vagal tone or impaired reflex control of the peripheral circulation. The most frequent type is **vasovagal syncope** or the "common faint," which is often initiated by a stressful, painful, or claustrophobic experience, especially in young women. Enhanced vagal tone with resulting hypotension is the cause of syncope in **carotid sinus hypersensitivity** and **postmicturition syncope;** vagal-induced sinus bradycardia, sinus arrest, and AV block are common accompaniments and may themselves be the cause of syncope.

Orthostatic (postural) hypotension is another common cause of vasodepressor syncope, especially in elderly patients; in diabetic patients or others with autonomic neuropathy; in patients with blood loss or hypovolemia; and in patients taking vasodilators, diuretics, and adrenergic-blocking medications. In addition, a syndrome of **chronic idiopathic orthostatic hypotension** exists primarily in older men. In most of these conditions, the normal vasoconstrictive response to assuming upright posture, which compensates for the abrupt decrease in venous return, is impaired.

Cardiogenic syncope can occur on a mechanical or arrhythmic basis. There is usually no prodrome; thus, injury secondary to falling is common. Mechanical problems that can cause syncope include aortic stenosis (where syncope may occur from autonomic reflex abnormalities or ventricular tachycardia), pulmonary stenosis, HCM, congenital lesions associated with pulmonary hypertension or right-to-left shunting, and LA myxoma obstructing the mitral valve. Episodes are commonly exertional or postexertional. More commonly, cardiac syncope is due to disorders of automaticity (sick sinus syndrome), conduction disorders (AV block), or tachyarrhythmias (especially ventricular tachycardia and SVT with rapid ventricular rate).

Clinical Findings

A. Symptoms and Signs

Vasovagal syncope often has a prodrome of vasodepressor premonitory symptoms, such as nausea, diaphoresis, tachycardia, and pallor. Episodes can be aborted by lying down or removing the inciting stimulus. Cardiogenic syncope by contrast is characteristically abrupt in onset, often resulting in injury, transient (lasting for seconds to a few minutes), and followed by prompt recovery of full consciousness. In orthostatic (postural) hypotension, a greater than normal decline (20 mm Hg) in BP immediately upon arising from the supine to the standing position is observed, with or without tachycardia depending on the status of autonomic (baroreceptor) function.

B. Diagnostic Tests

The evaluation for syncope depends on findings from the history and physical examination (especially orthostatic BP evaluation, auscultation of carotid arteries, and cardiac examination).

1. ECG—A resting ECG is recommended for all patients undergoing evaluation for syncope. High-risk findings on ECG include non-sinus rhythm, complete or partial left bundle branch block, and voltage criteria indicating LV hypertrophy. Patients with a normal initial evaluation, including unremarkable history and physical, absence of cardiac disease or significant comorbidities and normal baseline ECG may not need further testing. When initial evaluation suggests a possible cardiac arrhythmia, continuous ambulatory ECG monitoring, event recorder (for infrequent episodes), or a wearable or implantable cardiac monitor can be considered. Caution is required before attributing a patient's syncopal event to rhythm or conduction abnormalities observed during monitoring without concomitant symptoms. For instance, dizziness or syncope in older patients may be unrelated to incidentally observed bradycardia, sinus node abnormalities, or ventricular ectopy.

2. Autonomic testing—Tilt-table testing may be useful in patients with suspected vasovagal syncope where the diagnosis is unclear after initial evaluation, especially when syncope is recurrent. The hemodynamic response to tilting determines whether there is a *cardioinhibitory*, *vasodepressor*, or *mixed* response. The overall utility of the test is improved when there is a high pretest probability of neurally mediated syncope, since the sensitivity and specificity of the test in the general population is only moderate.

3. Electrophysiologic studies—Electrophysiologic study has limited role in the evaluation of syncope, particularly in patients without structural heart disease or when there is a low suspicion for arrhythmic etiology. In patients with ischemic heart disease, LV dysfunction, known conduction

disease or arrhythmia, electrophysiologic study may help elucidate the mechanism of syncope and guide treatment decisions. The diagnostic yield in patients with structural heart disease is approximately 50%.

Treatment

In patients with vasovagal syncope, treatment consists largely of education on the benign nature of the condition and counseling to avoid predisposing situations. *Counter-pressure maneuvers* (squatting, leg-crossing, abdominal contraction) can be helpful in limiting or terminating episodes. Medical therapy is reserved for patients with symptoms despite these measures. Midodrine is an alpha-agonist that can increase the peripheral sympathetic neural outflow and decrease venous pooling during vasovagal episodes and has been shown to reduce the frequency of syncopal episodes in small randomized trials. Fludrocortisone and beta-blockers have also been used but generally provide minimal benefit. SSRIs have shown some benefit in select patients. There is generally no role for permanent pacemaker implantation in patients with vasovagal syncope, with the possible exception of patients older than age 40 years with prolonged (longer than 3 seconds), symptomatic episodes of asystole documented on ambulatory monitoring. Pacemaker implantation based soley upon tilt-table–induced asystolic (cardioinhibitory) response is rarely indicated.

If symptomatic bradyarrhythmias or supraventricular tachyarrhythmias are detected and felt to be the cause of syncope, therapy can usually be initiated without additional diagnostic studies. Permanent pacing is indicated in patients with cardiogenic syncope and documented severe pauses (greater than 3 seconds), bradycardia, or high-degree AV block (second-degree Mobitz type II or complete heart block) when symptoms are correlated to the arrhythmia.

An important consideration in patients who have experienced syncope, symptomatic ventricular tachycardia, or aborted sudden death is to provide recommendations concerning **automobile driving restrictions**. Patients with syncope thought to be due to temporary factors (acute MI, bradyarrhythmias subsequently treated with permanent pacing, medication effect, electrolyte imbalance) should be advised after recovery not to drive for at least 1 week. Other patients with symptomatic ventricular tachycardia or aborted sudden death, whether treated pharmacologically, with an ICD or with ablation therapy, warrant longer driving restriction (3–6 months). Significant variability in legal restrictions exist depending on region and providers should be familiar with their local driving laws and restrictions and advise patients accordingly.

When to Refer

- Patients with syncope and underlying structural heart disease, documented arrhythmia, or conduction disturbance.
- Unclear etiology of syncope with high-risk features (heart failure, abnormal ECG findings, advanced age, multiple unexplained episodes).

Brignole M et al; ESC Scientific Document Group. 2018 ESC guidelines for the diagnosis and management of syncope. Eur Heart J. 2018;39:1883. [PMID: 29562304]

HEART FAILURE

ESSENTIALS OF DIAGNOSIS

- LV failure: Either due to systolic or diastolic dysfunction. Predominant symptoms are those of low cardiac output and congestion, including dyspnea.
- RV failure: Symptoms of fluid overload predominate; usually RV failure is secondary to LV failure.
- Assessment of LV function is a crucial part of diagnosis and management.
- Optimal management of chronic heart failure includes combination medical therapies, such as ACE inhibitors, aldosterone antagonists, and beta-blockers.

General Considerations

Heart failure is a common syndrome that is increasing in incidence and prevalence. Approximately 6 million patients in the United States have heart failure, with 8 million or more patients projected to have heart failure by 2030. Each year in the United States, 809,000 patients are discharged from the hospital with a diagnosis of heart failure. It is primarily a disease of aging, with over 75% of existing and new cases occurring in individuals over 65 years of age. Seventy-five percent of heart failure patients have antecedent hypertension. The prevalence of heart failure rises from less than 1% in individuals below 60 years to nearly 10% in those over 80 years of age.

Heart failure may be right-sided or left-sided (or both). Patients with **left heart failure** may have symptoms of low cardiac output and elevated pulmonary venous pressure; dyspnea is the predominant feature. Signs of fluid retention predominate in **right heart failure**. Most patients exhibit symptoms or signs of both right- and left-sided failure, and LV dysfunction is the primary cause of RV failure. Approximately half of patients with heart failure have **preserved LV systolic function** and usually have some degree of **diastolic dysfunction.** Patients with reduced or preserved systolic function may have similar symptoms and it may be difficult to distinguish clinically between the two based on signs and symptoms. In developed countries, CAD with resulting MI and loss of functioning myocardium (**ischemic cardiomyopathy**) is the most common cause of systolic heart failure. Systemic hypertension remains an important cause of heart failure and, even more commonly in the United States, an exacerbating factor in patients with cardiac dysfunction due to other causes, such as CAD. Several processes may present with **dilated** or **congestive cardiomyopathy,** which is characterized by LV or

biventricular dilation and generalized systolic dysfunction. These are discussed elsewhere in this chapter, but the most common are alcoholic cardiomyopathy, viral myocarditis (including infections by HIV; see also the COVID-19 section in Chapter 32), and dilated cardiomyopathies with no obvious underlying cause (idiopathic cardiomyopathy). Rare causes of dilated cardiomyopathy include infiltrative diseases (hemochromatosis, sarcoidosis, amyloidosis, etc), other infectious agents, metabolic disorders, cardiotoxins, and medication toxicity. Valvular heart diseases—particularly degenerative aortic stenosis and chronic aortic or mitral regurgitation—are not infrequent causes of heart failure. Persistent tachycardia, often related to atrial arrhythmias, can cause systolic dysfunction that may be reversible with controlling the rate. Diastolic cardiac dysfunction is associated with aging and related myocardial stiffening, as well as LVH, commonly resulting from hypertension. Conditions such as **hypertrophic** or **restrictive cardiomyopathy,** diabetes, and pericardial disease can produce the same clinical picture. Atrial fibrillation with or without rapid ventricular response may contribute to impaired LV filling.

Heart failure is often preventable by early detection of patients at risk and by early intervention. The importance of these approaches is emphasized by US guidelines that have incorporated a classification of heart failure that includes four stages. **Stage A** includes patients at risk for developing heart failure (such as patients with hypertension). In the majority of these patients, development of heart failure can be prevented with interventions such as the aggressive treatment of hypertension, modification of coronary risk factors, and reduction of excessive alcohol intake. **Stage B** includes patients who have structural heart disease but no current or previously recognized symptoms of heart failure. Examples include patients with previous MI, other causes of reduced systolic function, LVH, or asymptomatic valvular disease. Both ACE inhibitors and beta-blockers prevent heart failure in the first two of these conditions, and more aggressive treatment of hypertension and early surgical intervention are effective in the latter two. **Stages C** and **D** include patients with clinical heart failure and the relatively small group of patients who have become refractory to the usual therapies, respectively.

Clinical Findings

A. Symptoms

The most common symptom of patients with **left heart failure** is shortness of breath, chiefly exertional dyspnea at first and then progressing to orthopnea, paroxysmal nocturnal dyspnea, and rest dyspnea. Chronic nonproductive cough, which is often worse in the recumbent position, may occur. Nocturia due to excretion of fluid retained during the day and increased renal perfusion in the recumbent position is a common nonspecific symptom of heart failure, as is fatigue and exercise intolerance. These symptoms correlate poorly with the degree of cardiac dysfunction. Patients with **right heart failure** have predominate signs of fluid retention, with the patient exhibiting edema, hepatic congestion and, on occasion, loss of appetite and nausea due to edema of the gut or impaired GI perfusion and ascites. Surprisingly, some individuals with severe LV dysfunction will display few signs of left heart failure and appear to have isolated right heart failure. Indeed, they may be clinically indistinguishable from patients with right heart failure secondary to pulmonary disease.

Patients with acute heart failure from MI, myocarditis, and acute valvular regurgitation due to endocarditis or other conditions usually present with pulmonary edema. Patients with episodic symptoms may be having LV dysfunction due to intermittent ischemia. Patients may also present with acute exacerbations of chronic, stable heart failure. Exacerbations may be caused by alterations in therapy (or patient noncompliance), excessive salt and fluid intake, arrhythmias, excessive activity, pulmonary emboli, intercurrent infection, or progression of the underlying disease.

Patients with heart failure are often categorized by the NYHA classification as **class I** (asymptomatic), **class II** (symptomatic with moderate activity), **class III** (symptomatic with mild activity), or **class IV** (symptomatic at rest). This classification is important since some of the treatments are indicated based on NYHA classification.

B. Signs

Many patients with heart failure, including some with severe symptoms, appear comfortable at rest. Others will be dyspneic during conversation or minor activity, and those with long-standing severe heart failure may appear cachectic or cyanotic. The vital signs may be normal, but tachycardia, hypotension, and reduced pulse pressure may be present. Patients often show signs of increased sympathetic nervous system activity, including cold extremities and diaphoresis. Important peripheral signs of heart failure can be detected by examination of the neck, the lungs, the abdomen, and the extremities. RA pressure may be estimated through the height of the pulsations in the jugular venous system. With the patient at 45 degrees, measure the height of the pulsation about the sternal angle, and add 5 cm to estimate the height above the left atrium, with a pressure greater than 8 cm being abnormal. In addition to the height of the venous pressure, abnormal pulsations, such as regurgitant *v* waves, should be sought. Examination of the carotid pulse may allow estimation of pulse pressure as well as detection of aortic stenosis. Thyroid examination may reveal occult hyperthyroidism or hypothyroidism, which are readily treatable causes of heart failure. Crackles at the lung bases reflect transudation of fluid into the alveoli. Pleural effusions may cause bibasilar dullness to percussion. Expiratory wheezing and rhonchi may be signs of heart failure. Patients with severe right heart failure may have hepatic enlargement—tender or nontender—due to passive congestion. Systolic pulsations may be felt in tricuspid regurgitation. Sustained moderate pressure on the liver may increase jugular venous pressure (a positive **hepatojugular reflux** is an increase of greater than 1 cm, which correlates with elevated PCWP). Ascites may also be present. Peripheral pitting edema is a common sign in patients with right heart failure and may extend into the thighs and abdominal wall.

Cardinal cardiac examination signs are a parasternal lift, indicating pulmonary hypertension; an enlarged and sustained LV impulse, indicating LV dilation and hypertrophy; a diminished first heart sound, suggesting impaired contractility; and an S_3 gallop originating in the LV and sometimes the RV. An S_4 is usually present in diastolic heart failure. Murmurs should be sought to exclude primary valvular disease; secondary mitral regurgitation and tricuspid regurgitation murmurs are common in patients with dilated ventricles. In chronic heart failure, many of the expected signs of heart failure may be absent despite markedly abnormal cardiac function and hemodynamic measurements.

C. Laboratory Findings

A blood count may reveal anemia and a high red-cell distribution width (RDW), both of which are associated with poor prognosis in chronic heart failure through poorly understood mechanisms. Kidney function tests can determine whether cardiac failure is associated with impaired kidney function that may reflect poor kidney perfusion. CKD is another poor prognostic factor in heart failure and may limit certain treatment options. Serum electrolytes may disclose hypokalemia, which increases the risk of arrhythmias; hyperkalemia, which may limit the use of inhibitors of the renin–angiotensin system; or hyponatremia, an indicator of marked activation of the renin–angiotensin system and a poor prognostic sign. Thyroid function should be assessed to detect occult thyrotoxicosis or myxedema, and iron studies should be checked to test for hemochromatosis. In unexplained cases, appropriate biopsies may lead to a diagnosis of amyloidosis. Myocardial biopsy may exclude specific causes of dilated cardiomyopathy but rarely reveals specific reversible diagnoses.

Serum BNP is a powerful prognostic marker that adds to clinical assessment in differentiating dyspnea due to heart failure from noncardiac causes. Two markers—**BNP** and **NT-proBNP**—provide similar diagnostic and prognostic information. BNP is expressed primarily in the ventricles and is elevated when ventricular filling pressures are high. It is quite sensitive in patients with symptomatic heart failure—whether due to systolic or to diastolic dysfunction—but less specific in older patients, women, and patients with COPD. Studies have shown that BNP can help in emergency department triage in the diagnosis of acute decompensated heart failure, such that an NT-proBNP less than 300 pg/mL or BNP less than 100 pg/mL, combined with a normal ECG, makes heart failure unlikely. BNP is less sensitive and specific to diagnose heart failure in the chronic setting. BNP may be helpful in guiding the intensity of diuretic and a more consistent use of disease-modifying therapies, such as ACE inhibitors and beta-blockers, for the management of chronic heart failure. BNP, but not NT-proBNP, is increased by neprilysin inhibitors, since neprilysin degrades BNP. Thus, while NT-proBNP is still reliable, BNP should *not* be used to monitor degree of heart failure when patients are treated with sacubitril/valsartan. Worsening breathlessness or weight associated with a rising BNP (or both) might prompt increasing the dose of diuretics. However, there is no proven value in using serial natriuretic peptide measurements to guide therapy, as shown in the GUIDE-IT trial. Elevation of serum troponin, and especially of high-sensitivity troponin, is common in both chronic and acute heart failure, and it is associated with higher risk of adverse outcomes.

D. ECG and Chest Radiography

ECG may indicate an underlying or secondary arrhythmia, MI, or nonspecific changes that often include low voltage, intraventricular conduction defects, LVH, and nonspecific repolarization changes. Chest radiographs provide information about the size and shape of the cardiac silhouette. Cardiomegaly is an important finding and is a poor prognostic sign. Evidence of pulmonary venous hypertension includes relative dilation of the upper lobe veins, perivascular edema (haziness of vessel outlines), interstitial edema, and alveolar fluid. In acute heart failure, these findings correlate moderately well with pulmonary venous pressure. However, patients with chronic heart failure may show relatively normal pulmonary vasculature despite markedly elevated pressures. Pleural effusions are common and tend to be bilateral or right-sided.

E. Additional Studies

The clinical diagnosis of systolic myocardial dysfunction is often inaccurate. The primary confounding conditions are diastolic dysfunction of the heart with decreased relaxation and filling of the LV (particularly in hypertension and in hypertrophic states) and pulmonary disease.

The most useful test is the echocardiogram because it can differentiate heart failure with and without preserved LV systolic function. The echocardiogram can define the size and function of both ventricles and of the atria. LVEF is the most commonly used measurement to define systolic function. RV function is assessed by contractility and other measures, such as tricuspid annular plane systolic excursion. Echocardiography will also allow detection of pericardial effusion, valvular abnormalities, intracardiac shunts, and segmental wall motion abnormalities suggestive of old MI as opposed to more generalized forms of dilated cardiomyopathy.

Radionuclide angiography as well as cardiac MRI also measure LVEF and permit analysis of regional wall motion. These tests are especially useful when echocardiography is technically suboptimal, such as in patients with severe pulmonary disease. MRI can assess for presence of scar tissue and of infiltrative disease. When myocardial ischemia is suspected as a cause of LV dysfunction, as it should be unless there is another clear cause, stress testing or coronary angiography should be performed.

F. Cardiac Catheterization

In most patients with heart failure, clinical examination and noninvasive tests can determine LV size and function and valve function to support and refine the diagnosis. Left heart catheterization may be helpful to define the presence and extent of CAD, although CT angiography may also be appropriate, especially when the likelihood of coronary disease is low. Evaluation for coronary disease is particularly

important when LV dysfunction may be partially reversible by revascularization. The combination of angina or noninvasive evidence of significant myocardial ischemia with symptomatic heart failure is often an indication for coronary angiography if the patient is a potential candidate for revascularization. Right heart catheterization may be useful to select and monitor therapy in patients refractory to standard therapy.

Treatment: Heart Failure With Reduced LVEF

The treatment of heart failure is aimed at relieving symptoms, improving functional status, and preventing death and hospitalizations. Figure 10–10 outlines the role of the major pharmacologic and device therapies for heart failure with reduced LVEF (less than or equal to 40%). **The evidence of clinical benefit, including reducing death and hospitalization, as well as reducing sudden cardiac death, of most therapies is limited to patients with heart failure with reduced LVEF (40% or less).** The SGLT2 inhibitors, which reduce heart failure hospitalization for patients with preserved EF, are one *exception* to this general finding. It is now recognized that patients with mildly reduced EF (41–49%) may derive benefit from mineralocorticoid receptor antagonist and angiotensin receptor-neprilysin inhibitor (ARNI) (sacubitril/valsartan). Treatment of heart failure with preserved LVEF is aimed at improving symptoms and treating comorbidities. Achieving target (or maximally tolerated up to target) dosing to obtain the benefits of these treatments that have been shown in clinical trials is important (Table 10–12).

A. Correction of Reversible Causes

The major reversible causes of heart failure with reduced LVEF, also called **chronic systolic heart failure,** include valvular lesions, myocardial ischemia, uncontrolled hypertension, arrhythmias (especially persistent tachycardias), alcohol- or drug-induced myocardial depression, hypothyroidism, intracardiac shunts, and high-output states. Calcium channel blockers with negative inotropy (specifically verapamil or diltiazem), antiarrhythmic medications, thiazolidinediones, and NSAIDs may be important contributors to worsening heart failure. Some metabolic and infiltrative cardiomyopathies may be partially reversible, or their progression may be slowed; these include hemochromatosis, sarcoidosis, and amyloidosis. Once possible reversible components are being addressed, the measures outlined below are appropriate.

B. Pharmacologic Treatment

See also the following section Acute Heart Failure & Pulmonary Edema.

1. Diuretic therapy—Diuretics are the most effective means of providing symptomatic relief to patients with moderate to severe heart failure with dyspnea and fluid overload, for heart failure with either reduced or preserved LVEF. Few patients with symptoms or signs of fluid retention can be optimally managed without a diuretic. However, excessive diuresis can lead to electrolyte imbalance

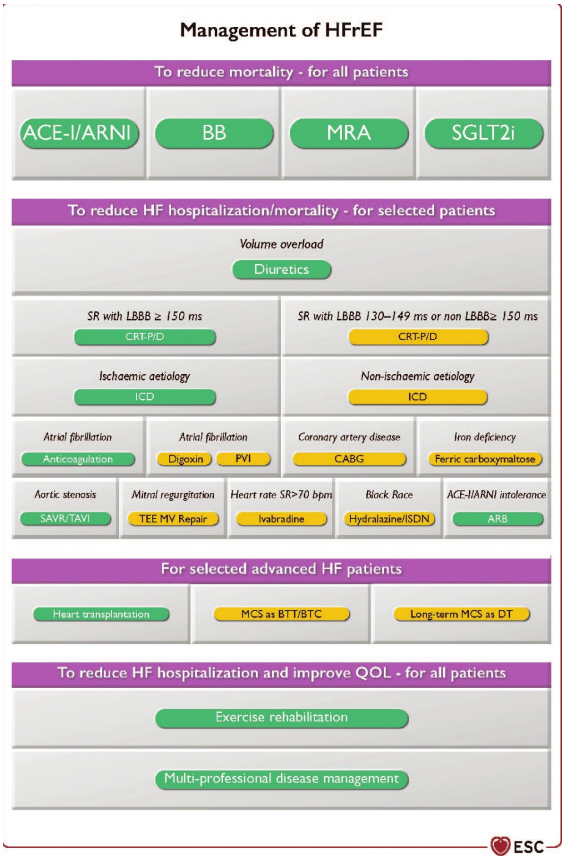


Figure 10–10. Strategic phenotypic overview of the management of heart failure with reduced EF. ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; b.p.m., beats per minute; BTC, bridge to candidacy; BTT, bridge to transplantation; CABG, coronary artery bypass graft; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; DT, destination therapy; HF, heart failure; HFrEF, heart failure with reduced EF; ICD, implantable cardioverter-defibrillator; ISDN, isosorbide dinitrate; LBBB, left bundle branch block; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; MV, mitral valve; PVI, pulmonary vein isolation; QOL, quality of life; SAVR, surgical aortic valve replacement; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SR, sinus rhythm; TAVI, transcatheter aortic valve replacement; TEE, transcatheter edge to edge. Color code for classes of recommendation: green for class of recommendation I; yellow for class of recommendation IIa. The figure shows management options with class I and IIa recommendations. (McDonagh TA et al; 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–3726, by permission of Oxford University Press.)

Table 10–12. Evidence-based doses of disease-modifying medications in key randomized trials in HFrEF or after MI (medications listed in alphabetical order within classes).

Medications	Starting Dose	Target Dose
ACE Inhibitors		
Captopril	6.25 mg three times daily	50 mg three times daily
Enalapril	2.5 mg twice daily	10–20 mg twice daily
Lisinopril	2.5–5.0 mg once daily	20–35 once daily
Ramipril	2.5 mg once daily	10 mg once daily
Trandolapril	0.5 mg once daily	4 mg once daily
Beta-Blockers		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily
Metoprolol succinate (CR/XL)	12.5–25 mg once daily	200 mg once daily
Nebivolol	1.25 once daily	10 mg once daily
ARBs		
Candesartan	4–8 mg once daily	32 mg once daily
Losartan	50 mg once daily	150 mg once daily
Valsartan	40 mg twice daily	160 mg twice daily
Aldosterone Antagonist		
Eplerenone	25 mg once daily	50 mg once daily
Spironolactone	25 mg once daily	50 mg once daily
ARNI		
Sacubitril/valsartan	49/51 mg twice daily	97/103 mg twice daily
I_f Channel Blocker		
Ivabradine	5 mg twice daily	7.5 mg twice daily
SGLT2 Inhibitors		
Dapagliflozin	10 mg once daily	10 mg once daily
Empagliflozin	10 mg once daily	10 mg once daily

ARNI, angiotensin receptor-neprilysin inhibitor; HFrEF, heart failure with reduced EF.

and neurohormonal activation. **A combination of a diuretic and an ACE inhibitor or ARNI should be the initial treatment in most symptomatic patients with heart failure and reduced LVEF, with the early addition of a beta-blocker.**

When fluid retention is mild, **thiazide diuretics** or a similar type of agent (hydrochlorothiazide, 25–100 mg; metolazone, 2.5–5 mg; chlorthalidone, 25–50 mg; etc) may be sufficient. Thiazide or related diuretics often provide better control of hypertension than short-acting loop agents. The thiazides are generally *ineffective* when the GFR falls below 30–40 mL/minute/1.73 m^2, a not infrequent occurrence in patients with severe heart failure. Metolazone maintains its efficacy down to a GFR of approximately 20–30 mL/minute/1.73 m^2. Adverse reactions include hypokalemia and intravascular volume depletion with resulting prerenal azotemia, skin rashes, neutropenia and thrombocytopenia, hyperglycemia, hyperuricemia, and hepatic dysfunction.

Patients with more severe heart failure should be treated with one of the oral **loop diuretics.** These include furosemide (20–320 mg daily), bumetanide (1–8 mg daily), and torsemide (20–200 mg daily). These agents have a rapid onset and a relatively short duration of action. In patients with preserved kidney function, two or more daily doses are preferable to a single larger dose. In acute situations or when GI absorption is in doubt, they should be given intravenously. Torsemide may be effective when furosemide is not, related to better absorption and a longer half life. Larger doses (up to 500 mg of furosemide or equivalent) may be required with severe renal impairment. The major adverse reactions include intravascular volume depletion, prerenal azotemia, and hypotension. Hypokalemia, particularly with accompanying digitalis therapy, is a major problem. Less common side effects include skin rashes, GI distress, and ototoxicity (the latter more common with ethacrynic acid and possibly less common with bumetanide).

The **oral potassium-sparing agents** are often useful in combination with the loop diuretics and thiazides, with the first choice being the aldosterone inhibitors spironolactone (12.5–100 mg daily) or eplerenone (25–100 mg daily). Aldosterone is often increased in heart failure. These medications spare loss of potassium, they have some diuretic effect (especially at higher doses), and they also improve clinical outcomes, including survival. Their onsets of action are slower than the other potassium-sparing agents, and spironolactone's side effects include gynecomastia and hyperkalemia. Combinations of potassium supplements or ACE inhibitors and potassium-sparing medications can increase the risk of hyperkalemia but have been used with success in patients with persistent hypokalemia.

Patients with refractory edema may respond to combinations of a loop diuretic and thiazide-like agents. Metolazone, because of its maintained activity with CKD, is the most useful agent for such a combination. Extreme caution must be observed with this approach, since massive diuresis and electrolyte imbalances often occur; 2.5 mg of metolazone orally should be added to the previous dosage of loop diuretic. In many cases this is necessary only once or twice a week, but dosages up to 10 mg daily have been used in some patients.

2. Inhibitors of the renin–angiotensin–aldosterone system—Inhibition of the renin–angiotensin–aldosterone system with ACE inhibitors should be part of the initial therapy of this syndrome based on their mortality benefits.

A. ACE inhibitors—At least seven ACE inhibitors have been shown to be effective for the treatment of heart failure or the related indication of postinfarction LV dysfunction (see Table 11–6). ACE inhibitors reduce mortality by approximately 20% in patients with symptomatic heart

failure and have also been shown to prevent hospitalizations, increase exercise tolerance, and reduce symptoms in these patients. As a result, ACE inhibitors generally should be part of first-line treatment of patients with symptomatic LV systolic dysfunction (EF less than 40%), usually in combination with a diuretic. They are also indicated for the management of patients with reduced EFs without symptoms because they prevent the progression to clinical heart failure.

Because ACE inhibitors may induce significant hypotension, particularly following the initial doses, they must be started with caution. Hypotension is most prominent in patients with already low BPs (systolic pressure less than 100 mm Hg), hypovolemia, prerenal azotemia (especially if it is diuretic induced), and hyponatremia (an indicator of activation of the renin–angiotensin system). These patients should generally be started at low dosages (captopril 6.25 mg orally three times daily, enalapril 2.5 mg orally daily, or the equivalent), but other patients may be started at twice these dosages. Within several days (for those with the markers of higher risk) or at most 2 weeks, patients should be questioned about symptoms of hypotension, and both kidney function and potassium levels should be monitored.

ACE inhibitors should be titrated to the dosages proved effective in clinical trials (captopril 50 mg three times daily, enalapril 10 mg twice daily, ramipril 10 mg daily, lisinopril 20 mg daily, or the equivalent) over a period of 1–3 months. Most patients will tolerate these doses. *Asymptomatic hypotension is not a contraindication to up-titrating or continuing ACE inhibitors.* Some patients exhibit increases in serum creatinine or potassium, but they do *not* require discontinuation if the levels stabilize—even at values as high as 3 mg/dL and 5.5 mEq/L, respectively. Kidney dysfunction is more frequent in patients with diabetes, older patients, and those with low systolic pressures, and these groups should be monitored more closely. The most common side effects of ACE inhibitors in heart failure patients are dizziness (often not related to the level of BP) and cough, though the latter is often due as much to heart failure or intercurrent pulmonary conditions as to the ACE inhibitor. ACE inhibitor–induced cough is more common in women than in men.

B. Angiotensin II receptor blockers—Another approach to inhibiting the renin–angiotensin–aldosterone system is the use of specific ARBs (see Table 11–6), which will decrease adverse effects of angiotensin II by blocking the AT_1 receptor. In addition, because there are alternative pathways of angiotensin II production in many tissues, the receptor blockers may provide more complete blockade of the AT_1 receptor.

However, these agents do *not* share the effects of ACE inhibitors on other potentially important pathways that produce increases in bradykinin, prostaglandins, and nitric oxide in the heart, blood vessels, and other tissues. ARBs, specifically candesartan or valsartan, provide important benefits as an alternative to ACE inhibitors in chronic heart failure with reduced LVEF. (A large trial of patients with chronic heart failure and preserved LVEF found no benefit from the ARB irbesartan.) **While they have the same level of recommendation in the guidelines, generally ACE inhibitors are preferred over ARBs for patients who tolerate them.**

C. Spironolactone and eplerenone—Inhibiting aldosterone has become a mainstay of management of symptomatic heart failure with reduced LVEF. The RALES trial compared spironolactone 25 mg daily with placebo in patients with advanced heart failure (current or recent class IV) already receiving ACE inhibitors and diuretics and showed a 29% reduction in mortality as well as similar decreases in other clinical end points. Based on the EMPHASIS-HF trial, the efficacy and safety of aldosterone antagonism—in the form of eplerenone, 25–50 mg orally daily—is established for patients with mild or moderate heart failure. Hyperkalemia was uncommon in severe heart failure clinical trial patients who received high doses of diuretic as maintenance therapy; however, hyperkalemia in patients taking spironolactone appears to be common in general practice. Potassium levels must be monitored closely during initiation of spironolactone (after 1 and 4 weeks of therapy) and periodically thereafter, particularly for patients with even mild degrees of kidney injury, and in patients receiving ACE inhibitors.

D. Combination sacubitril and valsartan—The most recently approved medication to improve clinical outcome in patients with heart failure and reduced LVEF is the combination of valsartan and sacubitril, called an **angiotensin receptor-neprilysin inhibitor (ARNI).** Compared to the ACE inhibitor enalapril, the ARNI was shown to reduce cardiovascular death and hospitalization for heart failure by 20% for patients with heart failure and reduced LVEF in a large randomized trial (PARADIGM-HF) of patients who had been taking an ACE inhibitor or ARB. Cardiovascular death itself was also reduced by 20%.

This evidence led to a class I recommendation by the ACC/AHA and the ESC guidelines for the use of **sacubitril/valsartan as a *replacement* for ACE inhibitors for patients with heart failure with reduced EF who remain symptomatic on an ACE inhibitor, beta-blocker, and mineralocorticoid inhibitor.** Patients with baseline systolic BP less than 100 mm Hg were not included in the PARADIGM trial, and symptomatic hypotension is more common with sacubitril/valsartan than ACE inhibitor. Sacubitril/valsartan can be safely started in the hospital for patients admitted with decompensated failure, once they are stable with systolic BP of at least 100 mm Hg and there has been a 36-hour washout period since the last dose of ACE inhibitor.

While there was some evidence of benefit, sacubitril/valsartan did not result in significant improvement in the primary outcome of total heart failure hospitalizations and cardiovascular death in the PARAGON-HF trial studying a population of patients with heart failure and preserved LVEF (45% or greater). However, the FDA has approved sacubitril/valsartan in this population, particularly for patients with EF "below normal," that is for EF less than 50% including patients with mildly reduced EF (41–49%).

3. Beta-blockers—Beta-blockers are part of the foundation of care of chronic heart failure based on their life-saving benefits. The mechanism of this benefit remains unclear, but it is likely that chronic elevations of catecholamines and sympathetic nervous system activity cause progressive myocardial damage, leading to worsening LV function and dilation. The primary evidence for this hypothesis is that over a period of 3–6 months, beta-blockers produce consistent substantial rises in EF (averaging 10% absolute increase) and reductions in LV size and mass.

Three medications have strong evidence of reducing mortality: **carvedilol** (a nonselective beta-1- and beta-2-receptor blocker), the beta-1-selective **extended-release agent metoprolol succinate** (but not short-acting metoprolol tartrate), and **bisoprolol** (beta-1-selective agent).

There is currently a strong recommendation that **stable patients (defined as having no recent deterioration or evidence of volume overload) with mild, moderate, and even severe heart failure should be treated with a beta-blocker unless there is a noncardiac contraindication.** In the COPERNICUS trial, carvedilol was both well tolerated and highly effective in reducing both mortality and heart failure hospitalizations in a group of patients with severe (NYHA class III or IV) symptoms, but care was taken to ensure that they were free of fluid retention at the time of initiation. In this study, one death was prevented for every 13 patients treated for 1 year—as dramatic an effect as has been seen with a pharmacologic therapy in the history of cardiovascular medicine. One trial comparing carvedilol and (short-acting) metoprolol tartrate (COMET) found significant reductions in all-cause mortality and cardiovascular mortality with carvedilol. Thus, patients with chronic heart failure should be treated with extended-release metoprolol succinate, bisoprolol, or carvedilol but *not* short-acting metoprolol tartrate.

Because even apparently stable patients may deteriorate when beta-blockers are initiated, initiation must be done gradually and with great care. Carvedilol is initiated at a dosage of 3.125 mg orally twice daily and may be increased to 6.25, 12.5, and 25 mg twice daily at intervals of approximately 2 weeks. The protocols for sustained-release metoprolol use were started at 12.5 or 25 mg orally daily and doubled at intervals of 2 weeks to a target dose of 200 mg daily (using the Toprol XL sustained-release preparation). Bisoprolol was administered at a dosage of 1.25, 2.5, 3.75, 5, 7.5, and 10 mg orally daily, with increments at 1- to 4-week intervals. More gradual up-titration is often more convenient and may be better tolerated. The SENIORS trial of 2135 patients found that nebivolol was effective in elderly patients (70 years and older) with chronic heart failure, although the evidence of degree of benefit was not as strong as with the three proven beta-blockers carvedilol, metoprolol succinate, or bisoprolol.

Patients should be instructed to monitor their weight at home as an indicator of fluid retention and to report any increase or change in symptoms immediately. Before each dose increase, patients should be seen and examined to ensure that there has not been fluid retention or worsening of symptoms. If heart failure worsens, this can usually be managed by increasing diuretic doses and delaying further increases in beta-blocker doses, though downward adjustments or discontinuation is sometimes required. Carvedilol, because of its beta-blocking activity, may cause dizziness or hypotension. This can usually be managed by reducing the doses of other vasodilators and by slowing the pace of dose increases.

4. SGLT2 inhibitors—Two large clinical trials of patients with type 2 diabetes have shown that inhibitors of SGLT2 substantially reduce the risk of cardiovascular death and hospitalization for heart failure for patients with reduced LVEF, with or without diabetes. Dapagliflozin also reduced all-cause mortality. Dagliflozin and empagliflozin reduce cardiovascular death and heart failure hospitalization, and they have been approved for treating heart failure with reduced LVEF. SGLT2 inhibitors also reduced kidney disease progression, and patients with eGFR of 20 mL/minute/1.73 m^2 have been included in these trials.

5. Digitalis glycosides—The efficacy of digitalis glycosides in reducing the symptoms of heart failure has been established in at least four multicenter trials that have demonstrated that digoxin withdrawal is associated with worsening symptoms and signs of heart failure, more frequent hospitalizations for decompensation, and reduced exercise tolerance. Digoxin should be considered for patients who remain symptomatic when taking diuretics and ACE inhibitors as well as for patients with heart failure who are in atrial fibrillation and require rate control. However, there is uncertainty about the safety of digoxin in this population with atrial fibrillation, especially with higher digoxin concentrations.

Digoxin has a half-life of 24–36 hours and is eliminated almost entirely by the kidneys. The oral maintenance dose may range from 0.125 mg three times weekly to 0.5 mg daily. It is lower in patients with kidney dysfunction, in older patients, and in those with smaller lean body mass. Although an oral loading dose of 0.75–1.25 mg (depending primarily on lean body size) over 24–48 hours may be given if an early effect is desired, in most patients with chronic heart failure it is sufficient to begin with the expected maintenance dose (usually 0.125–0.25 mg daily). Amiodarone, quinidine, propafenone, and verapamil are among the medications that may increase digoxin levels up to 100%. It is prudent to measure a blood level after 7–14 days (and at least 6 hours after the last dose was administered). Optimum serum digoxin levels are 0.7–1.2 ng/mL. Digoxin may induce ventricular arrhythmias, especially when hypokalemia or myocardial ischemia is present. Digoxin toxicity is discussed in Chapter 38.

6. Nitrates and hydralazine—Although ACE inhibitors, which have vasodilating properties, improve prognosis, such a benefit is not established with the direct-acting vasodilators. The combination of hydralazine and isosorbide dinitrate has been shown to *improve outcomes in Black persons*, but the effect is less clear than the well-established benefits of ACE inhibitors. ARBs or ARNIs have largely supplanted the use of the hydralazine–isosorbide dinitrate combination in ACE-intolerant patients.

See section Acute Myocardial Infarction with ST-Segment Elevation earlier in this chapter for a discussion

on the intravenous vasodilating medications and their dosages.

A. Nitrates—Intravenous vasodilators (sodium nitroprusside or nitroglycerin) are used primarily for acute or severely decompensated chronic heart failure, especially when accompanied by hypertension or myocardial ischemia. If neither of the latter is present, therapy is best initiated and adjusted based on hemodynamic measurements. The starting dosage for nitroglycerin is generally about 10 mcg/minute, which is titrated upward by 10–20 mcg/minute (to a maximum of 200 mcg/minute) until mean arterial pressure drops by 10%. Hypotension (BP less than 100 mm Hg systolic) should be avoided. For sodium nitroprusside, the starting dosage is 5–10 mcg/minute, with upward titration to a maximum dose of 400 mcg/minute.

Isosorbide dinitrate, 20–40 mg orally three times daily, and nitroglycerin ointment, 2%, 15–16 mg (1.4 inches; 1 inch = 15 mg) every 6–8 hours, appear to be equally effective, although the ointment is generally reserved for inpatient use only. The nitrates are moderately effective in relieving shortness of breath, especially in patients with mild to moderate symptoms, but less successful—probably because they have little effect on cardiac output—in advanced heart failure. Nitrate therapy is generally well tolerated, but headaches and hypotension may limit the dose of all agents. The development of tolerance to long-term nitrate therapy occurs. This is minimized by intermittent therapy, especially if a daily 8- to 12-hour nitrate-free interval is used, but probably develops to some extent in most patients receiving these agents. Transdermal nitroglycerin patches have no sustained effect in patients with heart failure and should *not* be used for this indication.

B. Hydralazine—Oral hydralazine is a potent arteriolar dilator; when used as a single agent, it has not been shown to improve symptoms or exercise tolerance during long-term treatment. The combination of nitrates and oral hydralazine produces greater hemodynamic effects as well as clinical benefits.

7. Ivabradine—Ivabradine inhibits the I_f channel in the sinus node and has the specific effect of slowing sinus rate. Ivabradine is approved by the FDA for use in stable patients with heart failure and heart rate of 70 beats/minute who are taking the maximally tolerated dose of beta-blockers or in patients in whom beta-blockers are contraindicated. It is approved by the European Medicines Agency for use in patients with a heart rate of 75 beats/minute or more. Both the US and the European guidelines give it a class IIa recommendation for patients in sinus rhythm with a heart rate of 70 beats/minute or more with an EF of 35% or less, and persisting symptoms despite treatment with an evidence-based dose of beta-blocker (or a maximum tolerated dose below that), ACE inhibitor (or ARB), and an aldosterone antagonist (or ARB). In a trial of patients with chronic angina, ivabradine did not reduce cardiovascular events, and there may have been more events with ivabradine (than placebo) in patients with symptomatic angina.

8. Vericiguat (a soluble guanylate cyclase stimulator)—In January 2021, the FDA approved vericiguat to reduce the risk of cardiovascular death and heart failure hospitalization following a hospitalization for heart failure in patients with chronic heart failure and LVEF less than 45%. The VICTORIA trial showed a modest but significant reduction in cardiovascular death and heart failure hospitalization with vericiguat, on top of other effective therapies, in this high-risk population.

9. Combination of medical therapies—Optimal management of chronic heart failure involves using combinations of proven life-saving therapies. In addition to ACE inhibitors and beta-blockers, patients who remain symptomatic should be considered for mineralocorticoid (aldosterone) receptor antagonists and for sacubitril/valsartan. This combination, titrated to full tolerated doses, with careful monitoring of kidney function and potassium, will provide the greatest pharmacologic benefit to the majority of patients with heart failure with reduced LVEF.

10. Treatments that may cause harm in heart failure with reduced LVEF—Several therapies should be *avoided,* when possible, in patients with systolic heart failure. These include thiazolidinediones (glitazones) that cause worsening heart failure, most calcium channel blockers (with the exception of amlodipine and felodipine), NSAIDs, and cyclooxygenase-2 inhibitors that cause sodium and water retention and renal impairment, and the combination of an ACE inhibitor, ARB, and aldosterone blocker that increases the risk of hyperkalemia.

11. Anticoagulation—Patients with LV failure and reduced EF are at somewhat increased risk for developing intracardiac thrombi and systemic arterial emboli. However, this risk appears to be primarily in patients who are in atrial fibrillation, who have had thromboemboli, or who have had a large recent anterior MI. In general, these patients should receive warfarin for 3 months following the MI. Other patients with heart failure have embolic rates of approximately two per 100 patient-years of follow-up, which approximates the rate of major bleeding, and routine anticoagulation is not warranted except in patients with prior embolic events or mobile LV thrombi. A clinical trial of low-dose rivaroxaban failed to show substantial benefit in patients with heart failure with reduced LVEF.

12. Antiarrhythmic therapy—Patients with moderate to severe heart failure have a high incidence of both symptomatic and asymptomatic arrhythmias. Although less than 10% of patients have syncope or presyncope resulting from ventricular tachycardia, ambulatory monitoring reveals that up to 70% of patients have asymptomatic episodes of nonsustained ventricular tachycardia. These arrhythmias indicate a poor prognosis independent of the severity of LV dysfunction, but many of the deaths are probably not arrhythmia related. Beta-blockers, because of their marked favorable effect on prognosis in general and on the incidence of sudden death specifically, should be initiated in these as well as all other patients with heart failure (see Beta-Blockers). Other evidence-based therapies for heart failure, including ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, and ARNIs, have all been shown to reduce sudden

cardiac death. Empiric antiarrhythmic therapy with amiodarone did not improve outcome in the SCD-HeFT trial, and most other agents are contraindicated because of their proarrhythmic effects in this population and their adverse effect on cardiac function. For patients with systolic heart failure and atrial fibrillation, a rhythm control strategy has not been shown to improve outcome compared to a rate control strategy and thus should be reserved for patients with a reversible cause of atrial fibrillation or refractory symptoms. Then, amiodarone is the medication of choice.

13. Statin therapy—Even though vascular disease is present in many patients with chronic heart failure, the role of statins has not been well defined in the heart failure population. The CORONA and the GISSI-HF trials show no benefits of statins in the chronic heart failure population.

C. Nonpharmacologic Treatment

1. Implantable cardioverter defibrillators (ICDs)—Indications for ICDs include not only patients with symptomatic or asymptomatic arrhythmias but also patients with chronic heart failure and LV systolic dysfunction who are receiving contemporary heart failure treatments, including beta-blockers. In the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II), 1232 patients with prior MI and an EF less than 30%, were randomized to an ICD or a control group. Mortality was 31% lower in the ICD group, which translated into 9 lives saved for each 100 patients who received a device and were monitored for 3 years. The Centers for Medicare and Medicaid Services provides reimbursement coverage to include patients with chronic heart failure and ischemic or nonischemic cardiomyopathy with an EF of 35% or less.

2. Biventricular pacing (resynchronization)—Many patients with heart failure due to systolic dysfunction have abnormal intraventricular conduction that results in dyssynchronous and hence inefficient contractions. Several studies have evaluated the efficacy of "multisite" pacing, using leads that stimulate the RV from the apex and the LV from the lateral wall via the coronary sinus. Patients with wide QRS complexes (generally 120 msec or more), reduced EFs, and moderate to severe symptoms have been evaluated. Results from trials with up to 2 years of follow-up have shown an increase in EF, improvement in symptoms and exercise tolerance, and reduction in death and hospitalization. The best responders to cardiac resynchronization therapy are patients with wider QRS, left bundle branch block, and nonischemic cardiomyopathy, and the lowest responders are those with narrow QRS and non–left bundle branch block pattern. Thus, as recommended in the 2013 European guidelines, resynchronization therapy is indicated for patients with class II, III, and ambulatory class IV heart failure, EF of 35% or less, and left bundle branch block pattern with QRS duration of 120 msec or more. Patients with non–left bundle branch block pattern and prolonged QRS duration may be considered for treatment.

3. Case management, diet, and exercise training—Thirty to 50 percent of heart failure patients who are hospitalized will be readmitted within 3–6 months. Strategies to prevent clinical deterioration, such as case management, home monitoring of weight and clinical status, and patient adjustment of diuretics, can prevent rehospitalizations and should be part of the treatment regimen of advanced heart failure. Involvement of a multidisciplinary team (rather than a single physician) and in-person (rather than just telephonic) communication appear to be important features of successful programs.

Patients should routinely practice moderate salt restriction (2–2.5 g sodium or 5–6 g salt per day). More severe sodium restriction is usually difficult to achieve and unnecessary because of the availability of potent diuretic agents.

Exercise training improves activity tolerance in significant part by reversing the peripheral abnormalities associated with heart failure and deconditioning. In severe heart failure, restriction of activity may facilitate temporary recompensation. A large trial showed no significant benefit (nor harm) from a structured exercise training program on death or hospitalization, although functional status and symptoms were improved. Thus, *in stable patients, a prudent increase in activity or a regular exercise regimen can be encouraged.* Indeed, a gradual exercise program is associated with diminished symptoms and substantial increases in exercise capacity.

4. Coronary revascularization—Since underlying CAD is the cause of heart failure in the majority of patients, coronary revascularization has been thought to be able to both improve symptoms and prevent progression. While the STITCH trial failed to show an overall survival benefit from CABG among patients with multivessel coronary disease who were candidates for CABG, but who also had heart failure and an LVEF of 35% or less, at 5 years, there was benefit at 10 years of follow-up. Thus, revascularization does appear warranted for some patients with heart failure, including those with more severe angina or left main coronary disease (excluded from the STITCH trial).

5. Cardiac transplantation—Because of the poor prognosis of patients with advanced heart failure, cardiac transplantation is widely used. Many centers have 1-year survival rates exceeding 80–90%, and 5-year survival rates above 70%. Infections, hypertension and kidney dysfunction caused by cyclosporine, rapidly progressive coronary atherosclerosis, and immunosuppressant-related cancers have been the major complications. The high cost and limited number of donor organs require careful patient selection early in the course.

6. Other surgical treatment options—Externally powered and implantable **ventricular assist devices** can be used in patients who require ventricular support either to allow the heart to recover or as a bridge to transplantation. The latest generation devices are small enough to allow patients unrestricted mobility and even discharge from the hospital. *Continuous flow* devices appear to be more effective than *pulsatile flow* devices. However, complications are frequent, including bleeding, thromboembolism, and infection, and the cost is very high, exceeding $200,000 in the initial 1–3 months.

Although 1-year survival was improved in the REMATCH randomized trial, all 129 patients died by 26 months. Newer-generation continuous flow pump ventricular assist devices have been shown to result in better survival than the first-generation pulsatile flow device used in REMATCH.

7. Palliative care—Despite the technologic advances of recent years, it should be remembered that many patients with chronic heart failure are elderly and have multiple comorbidities. Many of them will not experience meaningful improvements in survival with aggressive therapy. The goal of management for these patients and all those with serious illness should include symptomatic improvement and palliative care as they approach the end of life (see Chapter 5).

Treatment: Heart Failure With Preserved LVEF

Although half of all heart failure occurs among patients with normal LVEF, often with diastolic dysfunction, **the only therapy shown to reduce cardiovascular death or heart failure hospitalization in this population is empagliflozin.** The mainstays of treating heart failure with preserved EF are SGLT2 inhibitors and fluid management to avoid overload with diuretic therapy and to treat comorbidities like hypertension, diabetes, and arrhythmias.

A. Correction of Reversible Causes

Hypertension, pericardial disease, and atrial tachycardias are potentially reversible factors that can contribute to heart failure with preserved LVEF. Since tachycardia is associated with shorter overall diastolic filling time, controlling accelerated heart rate may be important. With effective treatment available for familial and wild-type transthyretin amyloid cardiomyopathy, this diagnosis should be considered for patients with unexplained heart failure with preserved EF.

B. Pharmacologic Treatment

1. Diuretic therapy—Diuretics are important to control symptoms of fluid overload in patients with heart failure with preserved LVEF, similar to symptoms from systolic heart failure.

2. Inhibitors of the renin-angiotensin-aldosterone system—ACE inhibitors and ARBs have *not* been shown to improve outcome in patients with heart failure and preserved LVEF, despite being good therapies for the comorbidity of hypertension. Sacubitril/valsartan does *not* substantially improve outcome in patients with heart failure and preserved LVEF. Spironolactone has *not* been shown to improve outcome in a large trial of patients with heart failure and preserved LVEF, but there may have been some benefit in patients enrolled in the Americas who had more clearly defined heart failure. Spironolactone should remain a therapeutic option, especially for patients who also have hypertension.

C. Nonpharmacologic Treatment

Unlike in patients with heart failure and reduced LVEF, ICD and resynchronization device treatments do *not* have a role in patients with preserved LVEF. Revascularization for patients with heart failure and preserved LVEF should be guided by the same considerations as for patients with heart failure with reduced LVEF.

Prognosis

Once manifest, heart failure with reduced LVEF carries a poor prognosis. Even with appropriate treatment, the 5-year mortality is approximately 50%. Mortality rates vary from less than 5% per year in those with no or few symptoms to greater than 30% per year in those with severe and refractory symptoms. These figures emphasize the critical importance of early detection and intervention. Higher mortality is related to older age, lower LVEF, more severe symptoms, CKD, and diabetes. The prognosis of heart failure has improved in the past two decades, probably at least in part because of the more widespread use of ACE inhibitors and beta-blockers, which markedly improve survival in those with heart failure with reduced LVEF.

When to Refer

Patients with new symptoms of heart failure not explained by an obvious cause should be referred to a cardiologist. Patients with continued symptoms of heart failure and reduced LVEF (35% or less) should be referred to a cardiologist for consideration of placement of an ICD or cardiac resynchronization therapy (if QRS duration is 120 msec or more, especially with left bundle branch block pattern).

When to Admit

- Patients with unexplained new or worsened symptoms or positive cardiac biomarkers concerning for acute myocardial necrosis.
- Patients with hypoxia, gross fluid overload, or pulmonary edema not readily resolved in an outpatient setting.

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ACUTE HEART FAILURE & PULMONARY EDEMA

ESSENTIALS OF DIAGNOSIS

- Acute onset or worsening of dyspnea at rest.
- Tachycardia, diaphoresis, cyanosis.
- Pulmonary rales, rhonchi; expiratory wheezing.
- Radiograph shows interstitial and alveolar edema with or without cardiomegaly.
- Arterial hypoxemia.

General Considerations

Typical causes of acute cardiogenic pulmonary edema include acute MI or severe ischemia, exacerbation of chronic heart failure, acute severe hypertension, AKI, acute volume overload of the LV (valvular regurgitation), and mitral stenosis. By far the most common presentation in developed countries is one of acute or subacute deterioration of chronic heart failure, precipitated by discontinuation of medications, excessive salt intake, myocardial ischemia, tachyarrhythmias (especially rapid atrial fibrillation), or intercurrent infection. Often in the latter group, there is preceding volume overload with worsening edema and progressive shortness of breath for which earlier intervention can usually avoid the need for hospital admission.

Clinical Findings

Acute pulmonary edema presents with a characteristic clinical picture of severe dyspnea, the production of pink, frothy sputum, and diaphoresis and cyanosis. Rales are present in all lung fields, as are generalized wheezing and rhonchi. Pulmonary edema may appear acutely or subacutely in the setting of chronic heart failure or may be the first manifestation of cardiac disease, usually acute MI, which may be painful or silent. Less severe decompensations usually present with dyspnea at rest, rales, and other evidence of fluid retention but without severe hypoxia.

Noncardiac causes of pulmonary edema include intravenous opioids, increased intracerebral pressure, high altitude, sepsis, medications, inhaled toxins, transfusion reactions, shock, and disseminated intravascular coagulation. These are distinguished from cardiogenic pulmonary edema by the clinical setting, history, and physical examination. Conversely, in most patients with cardiogenic pulmonary edema, an underlying cardiac abnormality can usually be detected clinically or by ECG, chest radiograph, or echocardiogram.

The chest radiograph reveals signs of pulmonary vascular redistribution, blurriness of vascular outlines, increased interstitial markings, and, characteristically, the butterfly pattern of distribution of alveolar edema. The heart may be enlarged or normal in size depending on whether heart failure was previously present. Assessment of cardiac function by echocardiography is important, since a substantial proportion of patients has normal EFs with elevated atrial pressures due to diastolic dysfunction. In cardiogenic pulmonary edema, BNP is elevated, and the PCWP is invariably elevated, usually over 25 mm Hg. In noncardiogenic pulmonary edema, the wedge pressure may be normal or even low.

Treatment

In full-blown pulmonary edema, the patient should be placed in a sitting position with legs dangling over the side of the bed; this facilitates respiration and reduces venous return. **Oxygen** is delivered by mask to obtain an arterial Po_2 greater than 60 mm Hg. Noninvasive pressure support ventilation may improve oxygenation and prevent severe CO_2 retention while pharmacologic interventions take effect. However, if respiratory distress remains severe, endotracheal intubation and mechanical ventilation may be necessary.

Morphine is highly effective in pulmonary edema and may be helpful in less severe decompensations when the patient is uncomfortable. The initial dosage is 2–8 mg intravenously (subcutaneous administration is effective in milder cases) and may be repeated after 2–4 hours. Morphine increases venous capacitance, lowering LA pressure, and relieves anxiety, which can reduce the efficiency of ventilation. However, morphine may lead to CO_2 retention by reducing the ventilatory drive. It should be avoided in patients with opioid-induced pulmonary edema, who may improve with opioid antagonists, and in those with neurogenic pulmonary edema.

Intravenous diuretic therapy (furosemide, 40 mg, or bumetanide, 1 mg—or higher doses if the patient has been receiving long-term diuretic therapy) is usually indicated even if the patient has not exhibited prior fluid retention. These agents produce venodilation prior to the onset of diuresis. The DOSE trial has shown that, for acute decompensated heart failure, bolus doses of furosemide are of similar efficacy as continuous intravenous infusion, and that higher-dose furosemide (2.5 times the prior daily dose) resulted in more rapid fluid removal without a substantially higher risk of kidney impairment.

Nitrate therapy accelerates clinical improvement by reducing both BP and LV filling pressures. Sublingual nitroglycerin or isosorbide dinitrate, topical nitroglycerin, or intravenous nitrates will ameliorate dyspnea rapidly prior to the onset of diuresis, and these agents are particularly valuable in patients with accompanying hypertension.

Intravenous nesiritide, a recombinant form of human BNP, is a potent vasodilator that reduces ventricular filling pressures and improves cardiac output. Its hemodynamic effects resemble those of intravenous nitroglycerin with a

more predictable dose–response curve and a longer duration of action. In clinical studies, nesiritide (administered as 2 mcg/kg by intravenous bolus injection followed by an infusion of 0.01 mcg/kg/minute, which may be up-titrated if needed) produced a rapid improvement in both dyspnea and hemodynamics. The primary adverse effect is hypotension, which may be symptomatic and sustained. Because most patients with acute heart failure respond well to conventional therapy, the role of nesiritide may be primarily in patients who continue to be symptomatic after initial treatment with diuretics and nitrates.

A randomized placebo-controlled trial of 950 patients evaluating intravenous milrinone in patients admitted for decompensated heart failure who had no definite indications for inotropic therapy showed no benefit in increasing survival, decreasing length of admission, or preventing readmission. In addition, rates of sustained hypotension and atrial fibrillation were significantly increased. Thus, the role of positive inotropic agents appears to be limited to patients with refractory symptoms and signs of low cardiac output, particularly if life-threatening vital organ hypoperfusion (such as deteriorating kidney function) is present. In some cases, dobutamine or milrinone may help maintain patients who are awaiting cardiac transplantation.

Bronchospasm may occur in response to pulmonary edema and may itself exacerbate hypoxemia and dyspnea. Treatment with inhaled beta-adrenergic agonists or intravenous aminophylline may be helpful, but both may also provoke tachycardia and supraventricular arrhythmias.

In most cases, pulmonary edema responds rapidly to therapy. When the patient has improved, the cause or precipitating factor should be ascertained. In patients without prior heart failure, evaluation should include echocardiography and, in many cases, cardiac catheterization and coronary angiography. Patients with acute decompensation of chronic heart failure should be treated to achieve a euvolemic state and have their medical regimen optimized. Generally, an oral diuretic and an ACE inhibitor should be initiated, with efficacy and tolerability confirmed prior to discharge. In selected patients, early but careful initiation of beta-blockers in low doses should be considered.

MYOCARDITIS & THE CARDIOMYOPATHIES

INFECTIOUS MYOCARDITIS

ESSENTIALS OF DIAGNOSIS

- Often follows an upper respiratory infection.
- May present with chest pain (pleuritic or nonspecific) or signs of heart failure.
- Echocardiogram documents cardiomegaly and contractile dysfunction. Initial heart size is generally normal with thickened walls.
- Myocardial biopsy, though not sensitive, may reveal a characteristic inflammatory pattern. MRI has a role in diagnosis.
- COVID-19 myocarditis impacts between 3% and 58% of people with COVID-19 based on underlying myocardial risk and imaging.

General Considerations

Cardiac dysfunction due to primary myocarditis is presumably caused by either an acute viral infection or a post viral immune response. Secondary myocarditis is the result of inflammation caused by nonviral pathogens, medications, chemicals, physical agents, or inflammatory diseases (such as SLE). The list of both infectious and noninfectious causes of myocarditis is extensive (Table 10–13).

Myopericarditis due to the coronavirus has been of particular concern during the COVID-19 pandemic. Much remains unknown. There is speculation that the SARS-CoV-2 spike protein may be able to bind to the ACE-2 membrane receptor on cardiomyocytes creating direct cellular injury and T-lymphocyte–mediated cytotoxicity augmented by a cytokine storm. This process activates more T cells and furthers a cycle of T-cell activation and further release of cytokines.

The currently accepted definition of myocarditis is biopsy dependent and includes the observation of 14 or more lymphocytes/mcL including up to 4 monocytes/mcL with the presence of 7 or more CD3-positive T lymphocytes/mcL. Injury can be **fulminant, subclinical,** or **chronic.** Both cellular and humoral inflammatory processes contribute to the progression to chronic injury, and there are subgroups that appear to benefit from immunosuppression.

Genetic predisposition is a likely factor in at least a few cases. Autoimmune myocarditis (eg, giant cell myocarditis) may occur with no identifiable viral infection. The heterogeneity of the clinical syndromes and the incomplete understanding of the immunopathology hinder a more complete understanding of the mechanisms involved.

Myocarditis following SARS-CoV-2 infection or vaccination have been reported in the medical literature. In both scenarios, younger male patients seem to be at highest risk for this overall rare event. With vaccination, the CDC reports rates of 13.3 myocarditis cases per 100,000 recipients of the Moderna vaccine and 2.7 cases per 100,000 recipients of the Pfizer-BioNTech vaccine; with natural COVID-19 infection, a rate of 150 cases of myocarditis per 100,000 people has been described. This variation in the myocarditis rates between the two vaccines is not understood and is the focus on ongoing research. With COVID-19, myocarditis appears to affect ethnic groups disproportionately with death rates highest among Black persons likely due to both an increase in comorbidities and health care disparities. In a German study of 100 patients who had recovered from COVID-19, cardiac MRI revealed some degree of abnormality in 78 patients, with inflammation noted in 60, independent of severity of the illness.

Table 10–13. Causes of myocarditis.

1. INFECTIOUS CAUSES
RNA viruses: Picornaviruses (coxsackie A and B, echovirus, poliovirus, hepatitis virus), orthomyxovirus (influenza), paramyxoviruses (respiratory syncytial virus, mumps), togaviruses (rubella), flaviviruses (dengue fever, yellow fever), SARS-CoV-2
DNA viruses: Adenovirus (A1, 2, 3, and 5), erythrovirus (Bi9V and 2), herpesviruses (human herpes virus 6 A and B, cytomegalovirus, Epstein-Barr virus, varicella-zoster), retrovirus (HIV)
Bacteria: Chlamydia (*Chlamydophila pneumoniae, C psittaci*), *Haemophilus influenzae*, *Legionella, Pneumophilia, Brucella, Clostridium, Francisella tularensis, Neisseria meningitis, Mycobacterium* (tuberculosis), *Salmonella, Staphylococcus, streptococcus* A, *Streptococcus pneumoniae,* tularemia, tetanus, syphilis, *Vibrio cholerae*
Spirocheta: *Borrelia recurrentis*, leptospira, *Treponema pallidum*
Rickettsia: *Coxiella burnetii, R rickettsii, R prowazekii*
Fungi: *Actinomyces, Aspergillus, Candida, Cryptococcus, Histoplasma, Nocardia*
Protozoa: *Entamoeba histolytica, Plasmodium falciparum, Trypanosoma cruzi, T burcei, T gondii, Leishmania*
Helminthic: *Ascaris, Echinococcus granulosus, Schistosoma, Trichenella spiralis, Wuchereria bancrofti*
2. NONINFECTIOUS CAUSES
Autoimmune diseases: Dermatomyositis, inflammatory bowel disease, rheumatoid arthritis, Sjögren syndrome, SLE, granulomatosis with polyangiitis, giant cell myocarditis
Medications: Aminophylline, amphetamine, anthracyclin, catecholamines, chloramphenicol, cocaine, cyclophosphamide, doxorubicin, 5-FU, mesylate, methysergide, phenytoin, trastuzumab, zidovudine
Hypersensitivity reactions due to medications: Azithromycin, benzodiazepines, clozapine, cephalosporins, dapsone, dobutamine, lithium, diuretics, thiazide, methyldopa, mexiletine, streptomycin, sulfonamides, NSAIDs, tetanus toxoid, tetracycline, tricyclic antidepressants
Hypersensitivity reactions due to venoms: Bee, wasp, black widow spider, scorpion, snake
Systemic diseases: Eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome), collagen diseases, sarcoidosis, Kawasaki disease, systemic sclerosis
Other: Heat stroke, hypothermia, transplant rejection, radiation injury

Schultheiss HP et al. The manage of myocarditis. Eur Heart J. 2011;32(21):2616–25, by permission of Oxford University Press and the European Society of Cardiology.

Clinical Findings

A. Symptoms and Signs

Patients may present several days to a few weeks after the onset of an acute febrile illness or a respiratory infection or they may present with heart failure without antecedent symptoms. The onset of heart failure may be gradual or may be abrupt and fulminant. In acute fulminant myocarditis, low output and shock may be present with severely depressed LV systolic function. The LV chamber size is typically not very enlarged. A pericardial friction rub may be present. In the European Study of Epidemiology and Treatment of Inflammatory Heart Disease, 72% of participants had dyspnea, 32% had chest pain, and 18% had arrhythmias. Pulmonary and systemic emboli may occur. Pleural-pericardial chest pain is common. Examination reveals tachycardia, a gallop rhythm, and other evidence of heart failure or conduction defects. At times, the presentation may mimic an acute MI with ST changes, positive cardiac markers, and regional wall motion abnormalities despite normal coronaries. Microaneurysms may also occur and may be associated with serious ventricular arrhythmias. It has been estimated that approximately 10% of all dilated cardiomyopathy patients have viral myocarditis as the cause.

B. ECG and Chest Radiography

ECG may show sinus tachycardia, other arrhythmias, nonspecific repolarization changes, and intraventricular conduction abnormalities. The presence of Q waves or left bundle branch block portends a higher rate of death or cardiac transplantation. Ventricular ectopy may be the initial and only clinical finding. The chest radiograph is nonspecific, but cardiomegaly is frequent, though not universal. Evidence for pulmonary venous hypertension is common and frank pulmonary edema may be present.

C. Diagnostic Studies

There is no specific laboratory finding that is consistently present, though the WBC count is usually elevated and the ESR and CRP usually are increased. Troponin I or T levels are elevated in about one-third of patients, but CK-MB is elevated in only 10%. Other biomarkers, such as BNP and NT-proBNP, are usually elevated. Echocardiography provides the most convenient way of evaluating cardiac function and can exclude many other processes. MRI with gadolinium enhancement reveals spotty areas of injury throughout the myocardium, but both T2- and T1-weighted images are needed to achieve optimal results; correlation with endomyocardial biopsy results is poor.

D. Endomyocardial Biopsy

Confirmation of myocarditis still requires histologic evidence. The AHA/ACC/ESC class I recommendations for biopsy are (1) in patients with heart failure, a normal-sized or dilated LV less than 2 weeks after onset of symptoms, and hemodynamic compromise; or (2) in patients with a dilated LV 2 weeks to 3 months after onset of symptoms, new ventricular arrhythmias or AV nodal block (Mobitz II or complete heart block) or who do not respond to usual care after 1–2 weeks. In some cases, the identification of inflammation without viral genomes by PCR suggests that immunosuppression might be useful. Because the cardiac involvement is often patchy, the diagnosis even with biopsy can be missed in up to one-half of cases.

Treatment & Prognosis

Patients with fulminant myocarditis may present with acute cardiogenic shock. Acute myocarditis has been

implicated as a cause of sudden death in 5–22% of such cases in athletes younger than 35 years. The ventricles are usually not dilated but thickened (possibly due to myxedema). There is a high death rate. Traditionally, there has been a paradox noted, wherein patients with fulminant myocarditis were thought to more likely fully recover after the event. Several recent observations have challenged this concept. Patients with subacute disease have a dilated cardiomyopathy and generally make an incomplete recovery. Those who present with chronic disease tend to have only mild dilation of the LV and eventually present with a more restrictive cardiomyopathy. Treatment is directed toward the clinical scenario with ACE inhibitors and beta-blockers if LVEF is less than 40%. NSAIDs should be used if myopericarditis-related chest pain occurs. Colchicine has been suggested if pericarditis predominates. Arrhythmias should be suppressed.

For COVID-19–related myocarditis, treatment is generally supportive. A 2020 review noted that of the attempted therapies, such as remdesivir, glucocorticoids, IL-6 inhibitors (tocilizumab), intravenous immunoglobulin (IVIG), and colchicine, only corticosteroids appeared to have any favorable effect on outcomes. The data are still incomplete, however, as of early 2022.

Specific antimicrobial therapy is indicated when an infecting agent is identified. Exercise should be limited during the recovery phase. Some experts believe digoxin should be avoided, and it likely has little value in this setting anyway. Controlled trials of immunosuppressive therapy with corticosteroids and IVIG have not suggested a benefit, though some recommend IVIG given at 2 g/kg over 24 hours in proven cases. Uncontrolled trials suggest that interferon might have a supportive role. Similarly, antiviral medication (such as pleconaril for enteroviruses) has been tried empirically. Studies are lacking as to when to discontinue the chosen therapy if the patient improves. Patients with fulminant myocarditis require aggressive short-term support, including an IABP or an LV assist device. If severe pulmonary infiltrates accompany the fulminant myocarditis, extracorporeal membrane oxygenation (ECMO) support may be temporarily required and has had notable success.

The question of what to do with the athlete in whom evidence of COVID-19 myocarditis has developed has led to a series of national discussions, some prompted by the cardiac MRI findings in young adults with minimal symptoms. The higher troponin levels associated with poorer outcomes have generally occurred only in hospitalized patients. The findings of an abnormal cardiac MRI have not consistently proven to result in any long-term cardiac injury. Table 10–14 outlines the suggested guidelines by a Task Force from the American College of Cardiology Sports and Exercise Section.

Table 10–14. American College of Cardiology Sports and Exercise Section Guidelines for athletes with COVID-19 myocarditis.

Myocarditis diagnosis if both of the following are present
• A clinical syndrome of < 3 months, duration
• Otherwise unexplained increase in serum troponin levels, ECG changes, arrhythmias, high-grade AV block, regional wall motion abnormalities, or pericardial effusion. MRI findings suggesting myocarditis including T1- or T2-weighted imaging or late gadolinium enhancement.
Sports eligibility after myocarditis
• Must obtain a resting echocardiogram, 24-hour ambulatory ECG monitoring, and an exercise ECG no earlier than 3–6 months after the illness (class I, LOE C)
• Can resume exercise training if ALL of the following are met (class IIa, LOE C)
– Normal ventricular function
– Serum markers of myocardial injury, heart failure, and inflammation have returned to normal
– Clinically relevant arrhythmias on ambulatory ECG monitoring or exercise ECG are absent.

AV, atrioventricular, LOE, level of evidence.

When to Refer

Patients in whom myocarditis is suspected should be seen by a cardiologist at a tertiary care center where facilities are available for diagnosis and therapies available should a fulminant course ensue. The facility should have ventricular support devices and transplantation options available.

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NONINFECTIOUS MYOCARDITIS

A variety of medications, illicit drugs, and toxic substances can produce acute or chronic myocardial injury; the clinical presentation varies widely. The phenothiazines, lithium, chloroquine, disopyramide, antimony-containing compounds, and arsenicals can also cause ECG changes, arrhythmias, or heart failure. Hypersensitivity reactions to sulfonamides, penicillins, and aminosalicylic acid as well as other medications can result in cardiac dysfunction.

Radiation can cause an acute inflammatory reaction as well as a chronic fibrosis of heart muscle, usually in conjunction with pericarditis.

Cardiotoxicity from cocaine may occur from coronary artery spasm, MI, arrhythmias, and myocarditis. A cocaine cardiomyopathy has also been described. Because many of these processes are believed to be mediated by cocaine's inhibitory effect on norepinephrine reuptake by sympathetic nerves, beta-blockers have been used in patients with fixed stenosis. In documented coronary spasm, calcium channel blockers and nitrates may be effective. Usual therapy for heart failure or conduction system disease is warranted when symptoms occur. Other recreational drug use has been associated with myocarditis in various case reports.

Systemic disorders are also associated with myocarditis. These include giant cell myocarditis, eosinophilic myocarditis, celiac disease, granulomatosis with polyangiitis, and sarcoidosis. A benefit from immunosuppressive therapy, especially in giant cell myocarditis has been suggested in a number of observational studies, including those directed primarily at T cells (ie, using muromonab-CD3). Treatment of eosinophilic myocarditis includes the use of high-dose corticosteroids and removal of the offending medication or underlying trigger, if known. Most studies suggest that HIV is only indirectly responsible for HIV cardiomyopathy, and other factors, gp 120 protein, adverse reaction to antiretroviral therapy, and opportunistic infections have been implicated more often. Epstein-Barr and herpes simplex viruses have been identified in some patients' myocardium.

The problem of cardiovascular side effects from cancer chemotherapy agents is an ever growing one and has spawned a new clinical area in cardiology called **cardio-oncology.** Anthracyclines (doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone) remain the cornerstone of treatment of many malignancies but may result in cardiomyopathy. Heart failure can be expected in 5% of patients treated with a cumulative dose of 400–450 mg/m^2, and this rate is doubled if the patient is over age 65. While symptoms and evidence for myocardial dysfunction usually appear within 1 year of starting therapy, late onset manifestation of heart failure may appear up to a decade later. The major mechanism of cardiotoxicity is thought to be due to oxidative stress inducing both apoptosis and necrosis of myocytes. There is also disruption of the sarcomere. This pathologic understanding is the rationale behind the superoxide dismutase mimetic and iron-chelating agent, dexrazoxane, to protect from the injury. The use of trastuzumab in combination with anthracyclines increases the risk of cardiac dysfunction up to 28%; this has been an issue since combined use of these agents is particularly effective in *HER2*-positive breast cancer. Other risk factors for patients receiving anthracyclines include the use of paclitaxel, concurrent radiation, and preexisting CVD (including hypertension, peripheral vascular disease, CAD, and diabetes). A summary of cardiotoxic cancer therapeutic agents and their role may be found in the 2019 AHA statement on cardio-oncology.

In patients receiving chemotherapy, it is important to look for subtle signs of cardiovascular compromise. Serial echocardiography, cardiac MR, or both can provide concrete data regarding LV function. Echo/Doppler myocardial global strain abnormalities may be the first abnormality observed (even prior to a drop in the LVEF) and assessment of the T2 signal from cardiac MRI may also provide early detection of cardiotoxicity. Biomarkers such as BNP or NT-proBNP may be of some value when serial measures are obtained. Other biomarkers may appear early in the course of myocardial injury (especially troponin and myeloperoxidase) and may allow for early detection of cardiotoxicity before other signs become evident. There is some evidence that beta-blocker therapy may reduce the negative effects on myocardial function. There are anecdotal data from animal models that NSAIDs may be harmful in patients with myocarditis. They should be avoided along with alcohol and strenuous physical exercise.

When to Refer

Many patients with myocardial injury from toxic agents can be monitored safely if ventricular function remains relatively preserved (EF greater than 40%) and no heart failure symptoms occur. Diastolic dysfunction may be subtle.

Once heart failure or a reduced LVEF becomes evident or significant conduction system disease becomes manifest, the patient should be evaluated and monitored by a cardiologist in case myocardial dysfunction worsens and further intervention becomes warranted.

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DILATED CARDIOMYOPATHY

ESSENTIALS OF DIAGNOSIS

- Symptoms and signs of heart failure.
- Echocardiogram confirms LV dilation, thinning, and global dysfunction.
- Severity of RV dysfunction critical in long-term prognosis.

General Considerations

Heart failure definitions have changed over the years and patients with a dilated cardiomyopathy are generally placed into the category of heart failure with reduced EF where the LVEF is defined as less than or equal to 40%. *In about half of the patients in this category, there is LV enlargement and it is this group that defines dilated cardiomyopathy.* This is a

large group of heterogeneous myocardial disorders characterized by reduced myocardial contractility in the absence of abnormal loading conditions such as with hypertension or valvular disease. The prevalence averages 36 cases/100,000 in the United States and accounts for approximately 10,000 deaths annually. Black patients are afflicted three times as often as White patients. The prognosis is poor with 50% mortality at 5 years once symptoms emerge.

The causes are multiple and diverse. Up to 20–35% have a familial etiology. It is common for hereditary causes to first present with conduction system disease prior to a reduced LVEF. A 2020 report of 2538 patients with a dilated cardiomyopathy in whom genetics were available suggested a clear association with at least 12 differing genes. Recent attention has focused particularly on the Lamin A/C genotype. While a large proportion of dilated cardiomyopathy causes are listed as idiopathic, it is likely that genetic variants may be responsible for many of these. Endocrine, inflammatory, and metabolic causes include obesity, diabetes, thyroid disease, celiac disease, SLE, acromegaly, and growth hormone deficiency. Toxic, drug-induced, and inflammatory causes are listed in the prior section. Nutritional diseases such as deficiency of thiamine, selenium, and carnitine have also been documented. Dilated cardiomyopathy may also be caused by prolonged tachycardia either from supraventricular arrhythmias, from very frequent PVCs (more than 15% of heart beats), or from frequent RV pacing. Dilated cardiomyopathy is also associated with HIV, Chagas disease, rheumatologic disorders, iron overload, sleep apnea, amyloidosis, sarcoidosis, chronic alcohol usage, ESKD, or cobalt exposure ("Quebec beer-drinkers, cardiomyopathy"). Peripartum cardiomyopathy and stress-induced disease (tako-tsubo) are discussed separately.

Clinical Findings

A. Symptoms and Signs

In most patients, symptoms of heart failure develop gradually. It is important to seek out a history of familial dilated cardiomyopathy and to identify behaviors that might predispose patients to the disease. The physical examination reveals rales, an elevated JVP, cardiomegaly, S_3 gallop rhythm, often the murmurs of functional mitral or tricuspid regurgitation, peripheral edema, or ascites. In severe heart failure, Cheyne-Stokes breathing, pulsus alternans, pallor, and cyanosis may be present.

B. ECG and Chest Radiography

The major findings are listed in Table 10–15. Sinus tachycardia is common. Other common abnormalities include

Table 10–15. Classification of the cardiomyopathies.

	Dilated	Hypertrophic	Restrictive
Frequent causes	Idiopathic, alcoholic, major catecholamine discharge, myocarditis, postpartum, chemotherapy, endocrinopathies, genetic diseases, burnt out HOCM, CAD, tachycardia-induced, cocaine	Hereditary syndrome, possibly chronic hypertension in older adults	Amyloidosis, post-radiation, post–open heart surgery, diabetes, endomyocardial fibrosis, Fabry disease, sarcoidosis
Symptoms	Left or biventricular heart failure	Dyspnea, chest pain, syncope	Dyspnea, fatigue, right heart failure > left heart failure
Physical examination	Cardiomegaly, S_3, elevated jugular venous pressure, rales	Sustained point of maximal impulse, S_4, variable systolic murmur, bisferiens carotid pulse	Elevated jugular venous pressure
ECG	ST–T changes, conduction abnormalities, ventricular ectopy	LVH, exaggerated septal Q waves	ST–T changes, conduction abnormalities, low voltage
Chest radiograph	Enlarged heart, pulmonary congestion	Mild cardiomegaly	Mild to moderate cardiomegaly
Echocardiogram, nuclear studies, MRI, PET, CT	LV dilation and dysfunction	LVH, asymmetric septal or other myocardial wall thickness > 15 mm, small LV size, normal or supranormal function, systolic anterior mitral motion, diastolic dysfunction. May be nonobstructive or apical	Small or normal LV size, normal or mildly reduced LV function. Gadolinium hyperenhancement on MRI
Cardiac catheterization	LV dilation and dysfunction, high diastolic pressures, low cardiac output. Coronary angiography important to exclude ischemic cause	Small, hypercontractile LV, dynamic outflow gradient, diastolic dysfunction	High diastolic pressure, "square root" sign, normal or mildly reduced LV function

HOCM, hypertrophic obstructive cardiomyopathy.

left bundle branch block and ventricular or atrial arrhythmias. The chest radiograph reveals cardiomegaly, evidence for left and/or right heart failure, and pleural effusions (right more frequently than left).

C. Diagnostic Studies

In the 2017 AHA/ACCF heart failure guideline focused update, patients with dyspnea should have a BNP or NT-proBNP measured to help establish prognosis and disease severity (class I, level of evidence [LOE] A).

An echocardiogram is indicated to exclude unsuspected valvular or other lesions and confirm the presence of ventricular dilatation, reduced LV systolic function and associated RV systolic dysfunction, or pulmonary hypertension. Mitral Doppler inflow patterns also help in the diagnosis of concomitant diastolic dysfunction. Color flow Doppler can reveal tricuspid or mitral regurgitation, and continuous Doppler can estimate PA pressures. Intracavitary thrombosis is occasionally seen. Exercise or pharmacologic stress myocardial perfusion imaging may uncover underlying coronary disease. Radionuclide ventriculography provides a noninvasive measure of the EF and both RV and LV wall motion, though its use has been supplanted by cardiac MRI in most institutions. Cardiac MRI is particularly helpful in inflammatory or infiltrative processes, such as sarcoidosis or hemochromatosis, and is the diagnostic study of choice for RV dysplasia. MRI can also help define an ischemic etiology by noting gadolinium hyperenhancement consistent with myocardial scar from infarction or prior myocarditis. Cardiac catheterization is seldom of specific value unless myocardial ischemia is suspected, although right heart catheterization should be considered to help guide therapy when the clinical syndrome is not clear cut (class I indication, LOE C). Myocardial biopsy is rarely useful in establishing the diagnosis, although occasionally the underlying cause (eg, sarcoidosis, hemochromatosis) can be discerned. Its use is considered a class IIa indication with LOE of C. It should not be used routinely. Biopsy is most useful in transplant rejection.

Treatment

The management of heart failure is outlined in the section on heart failure. Standard therapy includes control of BP and of contributing factors such as obesity, smoking, diabetes or potentially cardiotoxic agents. All patients with a remote history of MI or acute coronary syndrome and reduced LVEF should be given ACE inhibitors, ARBs, or sacubitril/valsartan. Beta-blockers should be included in this population as well. **All patients with dilated cardiomyopathy regardless of etiology should be treated with beta-blockers and ACE inhibitors. If still symptomatic, aldosterone antagonists should be added, and ARNI used instead of an ACE inhibitor or ARB.** The use of the combination of all three of ACE inhibition, ARB, and aldosterone antagonists can create harm, though, and is discouraged due to concerns for hyperkalemia. Calcium channel blockers should be avoided except as necessary to control ventricular response in atrial fibrillation or flutter. If congestive symptoms are present, diuretics and an aldosterone antagonist should be added. In patients with class II–IV heart failure symptoms, an aldosterone receptor antagonist should be added when the LVEF is less than 35% (unless contraindicated). Care in the use of mineralocorticoid receptor antagonists is warranted when the GFR is less than 30 mL/minute/1.73 m^2 or when the potassium is elevated. All patients with diabetes should be taking mineralocorticoid antagonists if the LVEF is less than or equal to 40%. Systemic BP control is extremely important. Use of the angiotensin receptor-neprilysin inhibitor, sacubitril/valsartan, has been approved for NYHA Heart Failure of Functional class II–IV. If the resting heart rate is greater than 70 beats per minute, the LVEF is less than 35%, and the patient has chronic stable heart failure, the use of ivabradine to slow the heart rate has also been approved. Ivabradine should not replace other beta-blockers, however. Digoxin is a second-line medication but remains favored as an adjunct by some clinicians; digoxin may be beneficial to reduce recurrent hospitalizations and to control the ventricular response in atrial fibrillation in sedentary patients. Given the question of abnormal nitric oxide utilization in Blacks, the use of hydralazine-nitrate combination therapy is recommended in this population. Sodium restriction is helpful, especially in acute heart failure. Continuous positive airway pressure can improve LV function in patients with sleep apnea.

When atrial fibrillation is present, heart rate control is important if sinus rhythm cannot be established or maintained. There are few data, however, to suggest an advantage of sinus rhythm over atrial fibrillation on long-term outcomes. Many patients may be candidates for cardiac synchronization therapy with biventricular pacing if there is significant mitral regurgitation and the QRS width is greater than 150 msec.

To help prevent sudden death, an ICD is reasonable (class IIa, LOE B) in asymptomatic ischemic cardiomyopathy patients with an LVEF of less than 30% on appropriate medical therapy (at least 3 months post-MI). Cardiac rehabilitation and exercise training have consistently been found to improve clinical status.

Few cases of cardiomyopathy are amenable to specific therapy for the underlying cause. Alcohol use should be discontinued, since there is often marked recovery of cardiac function following a period of abstinence in alcoholic cardiomyopathy. Endocrine causes (hyperthyroidism or hypothyroidism, acromegaly, and pheochromocytoma) should be treated. Immunosuppressive therapy is not indicated in chronic dilated cardiomyopathy. There are some patients who may benefit from implantable LV assist devices either as a bridge to transplantation or as a temporary measure until cardiac function returns. LV assist devices can be considered as *destination therapy* in patients who are not candidates for cardiac transplantation. Arterial and pulmonary emboli are more common in dilated cardiomyopathy than in ischemic cardiomyopathy, and suitable candidates may benefit from long-term anticoagulation. All patients with atrial fibrillation should be so treated. DOACs are preferred over warfarin unless there is associated mitral stenosis. Either warfarin or a DOAC should be

considered when a mobile LV thrombus is observed on the echocardiogram.

Prognosis

The prognosis of dilated cardiomyopathy without clinical heart failure is variable, with some patients remaining stable, some deteriorating gradually, and others declining rapidly. Once heart failure is manifest, the natural history is similar to that of other causes of heart failure, with an annual mortality rate of around 11–13%. The underlying cause of heart failure has prognostic value in patients with unexplained cardiomyopathy. Patients with peripartum cardiomyopathy or stress-induced cardiomyopathy appear to have a better prognosis than those with other forms of cardiomyopathy. Patients with cardiomyopathy due to infiltrative myocardial diseases, HIV infection, or doxorubicin therapy have an especially poor prognosis.

When to Refer

Patients with new or worsening symptoms of heart failure with dilated cardiomyopathy should be referred to a cardiologist. Patients with continued symptoms of heart failure and reduced LVEF (35% or less) should be referred for consideration of placement of an ICD or cardiac resynchronization therapy (if QRS duration is 150 msec or more, especially with a left bundle branch block pattern). Patients with advanced refractory symptoms should be referred for consideration of heart transplant or LV assist device therapy.

When to Admit

Patients with hypoxia, fluid overload, or pulmonary edema not readily resolved in an outpatient setting should be admitted.

Mazzarotto F et al. Reevaluating the genetic contribution of monogenetic dilated cardiomyopathy. Circulation. 2020;141:387. [PMID: 31983221]

Rosenbaum AN et al. Genetics of dilated cardiomyopathy: practical implications for heart failure management. Nat Rev Cardiol. 2020;17:286. [PMID: 31605094]

STRESS CARDIOMYOPATHY

ESSENTIALS OF DIAGNOSIS

- Occurs after a major catecholamine discharge.
- Acute chest pain or shortness of breath.
- Predominately affects postmenopausal women.
- Presents as an acute anterior MI, but coronaries normal at cardiac catheterization.
- Imaging reveals apical LV ballooning due to anteroapical stunning of the myocardium.
- Most patients recover completely, although there are complications similar to MI.

General Considerations

Stress cardiomyopathy (**tako-tsubo syndrome**) generally follows a high catecholamine surge. The resulting shape of the LV acutely suggests a rounded ampulla form similar to a Japanese octopus pot (tako-tsubo pot). Mid-ventricular ballooning has also been described. The key feature is that the myocardial stunning that occurs does *not* follow the pattern suggestive of coronary ischemia (even though about 15% of patients will have coexisting CAD, and some may have concomitant plaque rupture MI). Over two-thirds of patients report a prior stressful event, either emotional or physical, including hypoglycemia, lightning strikes, earthquakes, postventricular tachycardia, during alcohol withdrawal, following surgery, during hyperthyroidism, after stroke, and following emotional stress ("broken-heart syndrome"). Virtually any event that triggers excess catecholamines has been implicated in a wide number of case reports. Pericarditis and even tamponade have been described in isolated cases. Recurrences have also been described. In Western countries it predominantly affects women (up to 90%), primarily postmenopausal. Among patients with stress cardiomyopathy, compared to patients with acute coronary syndrome, there are more neurologic and psychiatric disorders. Patients with COPD, migraines, or affective disorders who take beta-agonists may have an increased risk of a poor outcome. The prognosis was initially thought to be benign, but subsequent studies have demonstrated that *both short-term mortality and long-term mortality are higher than thought.* Indeed, mortality reported during the acute phase in hospitalized patients is approximately 4–5%, a figure comparable to that of STEMI in the era of primary percutaneous coronary interventions. Approximately 10% of patients will have cardiac and neurologic adverse outcomes over the next year.

The structures that mediate the stress response are in both the central and autonomic nervous systems. Acute stressors induce brain activation, increasing bioavailability of cortisol and catecholamine. Both circulating epinephrine and norepinephrine released from adrenal medullary chromaffin cells and norepinephrine released locally from sympathetic nerve terminals are significantly increased. This catecholamine surge leads to myocardial damage through multiple mechanisms, including, direct catecholamine toxicity, adrenoceptor-mediated damage, epicardial and microvascular coronary vasoconstriction and/or spasm, and increased cardiac workload. The relative preponderance among postmenopausal women suggests that estrogen deprivation may be facilitating, possibly via endothelial dysfunction.

Clinical Findings

A. Symptoms and Signs

The symptoms are similar to any acute coronary syndrome. Typical angina and dyspnea are usually present. Syncope is rare, although arrhythmias are not uncommon.

B. ECG and Chest Radiography

The ECG reveals ST-segment elevation as well as deep anterior T-wave inversion. The chest radiograph is either

normal or reveals pulmonary congestion. The dramatic T-wave inversions gradually resolve over time.

C. Diagnostic Studies

The echocardiogram reveals LV apical dyskinesia usually not consistent with any particular coronary distribution. The urgent cardiac catheterization reveals the LV apical ballooning in association with normal coronaries. Initial cardiac enzymes are positive but often taper quickly. In almost all cases, MRI hyperenhancement studies reveal no long-term scarring.

Treatment

Immediate therapy is similar to any acute MI. Initiation of long-term therapy depends on whether LV dysfunction persists. Most patients receive aspirin, beta-blockers, and ACE inhibitors until the LV fully recovers. Despite the presumed association with high catecholamines, the use of ACE inhibitors or ARBs, but not beta-blockers, has been associated with improved long-term survival. See Treatment of Heart Failure With Reduced LVEF.

Prognosis

The rate of severe in-hospital complications, including shock and death, appear to be similar between those with an acute coronary syndrome and tako-tsubo. Overall, prognosis is good unless there is a serious complication (such as mitral regurgitation, ventricular rupture, or ventricular tachycardia). Recovery of the LVEF is expected in most cases after a period of days to weeks.

When to Refer

All patients with an acute coronary syndrome should be urgently seen by a cardiologist for further evaluation and monitored until resolution of the ventricular dysfunction.

HYPERTROPHIC CARDIOMYOPATHY

ESSENTIALS OF DIAGNOSIS

- May present with dyspnea, chest pain, syncope.
- Though LV outflow gradient is classic, symptoms are primarily related to diastolic dysfunction.
- Echocardiogram is diagnostic. Any area of LV wall thickness > 1.5 cm defines the disease.
- Increased risk of sudden death.

General Considerations

In 2020, an ACC/AHA joint committee on clinical practice guidelines issued updated guidelines for the diagnosis and treatment of HCM. The guidelines address many clinical scenarios and provide a host of clinically relevant suggestions. HCM is noted when there is LVH unrelated to any pressure or volume overload. The definition has evolved over time; while it traditionally was defined by LV outflow obstruction due to septal hypertrophy, currently it is considered present any time that *any portion of LV wall is measured at more than 1.5 cm thick on an echocardiogram.* This allows for many forms to be considered that do not create LV outflow obstruction. The increased wall thickness reduces LV systolic stress, increases the EF, and can result in an "empty ventricle" at end-systole. The interventricular septum may be disproportionately involved (**asymmetric septal hypertrophy**), but in some cases the hypertrophy is localized to the mid-ventricle or to the apex. In a normal heart, the LV apex may be paper thin; in HCM, the LV obstruction may trap blood just above the apex and the LV pressure may be very high there. This can result in the apex becoming aneurysmal. The LV outflow tract is usually narrowed during systole due to the hypertrophied septum and systolic anterior motion of the mitral valve occurs as the anterior mitral valve leaflet is pulled into the LV outflow. The obstruction is worsened by factors that increase myocardial contractility (sympathetic stimulation, digoxin, and postextrasystolic beat) or that decrease LV filling (Valsalva maneuver, peripheral vasodilators). The amount of obstruction is preload and afterload dependent and can vary from day to day. The consequence of the hypertrophy is *elevated LV diastolic pressures* rather than systolic dysfunction. Rarely, systolic dysfunction develops late in the course of the disease. The LV is usually more involved than the RV, and the atria are frequently significantly enlarged.

HCM is inherited as an autosomal-dominant trait with variable penetrance and is caused by mutations of one of a large number of genes, most of which code for myosin heavy chains or proteins regulating calcium handling. The prognosis is related to the specific gene mutation. Patients usually present in early adulthood. Elite athletes may demonstrate considerable hypertrophy that can be confused with HCM, but generally diastolic dysfunction is not present in the athlete and this finding helps separate pathologic disease from **athletic hypertrophy**. The apical variety is particularly common in those of Asian descent. A **HCM in older adults** (usually in association with hypertension) has also been defined as a distinct entity (often a sigmoid interventricular septum is noted with a knob of cardiac muscle below the aortic valve). Mitral annular calcification is often present. Mitral regurgitation is variable and often dynamic, depending on the degree of outflow tract obstruction.

Clinical Findings

A. Symptoms and Signs

The most frequent symptoms are dyspnea and chest pain. Syncope is also common and is typically postexertional, when diastolic filling diminishes due to fluid loss and tachycardia increasing LV outflow tract obstruction. Residual circulating catecholamines accentuate the changes. Arrhythmias are an important problem. Atrial fibrillation is a long-term consequence of chronically elevated LA pressures and is a poor prognostic sign. Ventricular arrhythmias are also common, and sudden death may occur, often after extraordinary exertion.

Features on physical examination include a bisferiens carotid pulse, triple apical impulse (due to the prominent atrial filling wave and early and late systolic impulses), and a loud S_4. The JVP may reveal a prominent *a* wave due to reduced RV compliance. In cases with LV outflow obstruction, a loud systolic murmur is present along the left sternal border that increases with upright posture or Valsalva maneuver and decreases with squatting. These maneuvers help differentiate the murmur of HCM from that of aortic stenosis. In HCM, reducing the LV volume *increases* the outflow obstruction and the murmur intensity; whereas in valvular aortic stenosis, reducing the stroke volume across the valve *decreases* the murmur. Mitral regurgitation is frequently present as well.

B. ECG and Chest Radiography

LVH is nearly universal in symptomatic patients, though entirely normal ECGs are present in up to 25%, usually in those with localized hypertrophy. Exaggerated septal Q waves inferolaterally may mimic MI. The chest radiograph is often unimpressive. Unlike with aortic stenosis, the ascending aorta is not dilated.

C. Diagnostic Studies

The echocardiogram is diagnostic, revealing LVH (involving the septum more commonly than the posterior walls), systolic anterior motion of the mitral valve, early closing followed by reopening of the aortic valve, a small and hypercontractile LV, and delayed relaxation and filling of the LV during diastole. The septum is usually 1.3–1.5 times the thickness of the posterior wall. Septal motion tends to be reduced. Doppler ultrasound reveals turbulent flow and a dynamic gradient in the LV outflow tract and, commonly, mitral regurgitation. Abnormalities in the diastolic filling pattern are present in 80% of patients.

Echocardiography can usually differentiate the disease from ventricular noncompaction, a congenital myocardial disease pattern with marked trabeculation that partially fills the LV cavity. Myocardial perfusion imaging may suggest septal ischemia in the presence of normal coronary arteries. Cardiac MRI confirms the hypertrophy and contrast enhancement frequently reveals evidence of scar at the junction of the RV attachment to the interventricular septum. Cardiac catheterization confirms the diagnosis and defines the presence or absence of CAD. Frequently, coronary arterial bridging (squeezing of the coronary in systole) occurs, especially in the septal arteries. Exercise studies are recommended to assess for ventricular arrhythmias and to document the BP response. Loop monitoring is recommended for determination of ventricular ectopy.

Treatment

Beta-blockers should be the initial medication in symptomatic individuals, especially when dynamic outflow obstruction is noted on the echocardiogram. The resulting slower heart rates assist with diastolic filling of the stiff LV. Dyspnea, angina, and arrhythmias respond in about 50% of patients. Calcium channel blockers, especially verapamil, have also been effective in symptomatic patients. Verapamil or nondihydropyridine calcium channel blockers, such as diltiazem, are class I recommendations. Their effect is due primarily to improved diastolic function; however, their vasodilating actions can also increase outflow obstruction and cause hypotension. Verapamil should not be used if there is hypotension or a resting gradient of over 100 mm Hg. Disopyramide is also effective because of its negative inotropic effects; it is usually used as an addition to the medical regimen rather than as primary therapy or to help control atrial arrhythmias. Oral diuretics are frequently necessary due to the high LV diastolic pressure and elevated LA pressures but should be used with caution to avoid dehydration that would increase obstruction. Digoxin is relatively contraindicated, except rarely for rate control in atrial fibrillation. For acute hypotension that does not respond to fluids, phenylephrine may be considered. In HCM patients without outflow obstruction, similar treatment should be used only if symptomatic and the use of oral diuretics is safer. In a very small number of these patients, apical myomectomy may be considered.

Patients do best in sinus rhythm, and atrial fibrillation should be aggressively treated with antiarrhythmics or radiofrequency ablation. DOACs are preferred over warfarin if atrial fibrillation occurs. Patients with HCM should be treated regardless of their CHA_2DS_2-VASc score.

The 2020 AHA/ACC guidelines recommend a preventive ICD for HCM patients with documented cardiac arrest or sustained ventricular tachycardia (class I). It is a class IIa recommendation for an ICD if there are one or more of the following risk factors: (1) sudden death in one or more first-degree or close relative 50 years of age or younger, (2) any LV wall greater than or equal to 30 mm, (3) any recent syncope likely to have been arrhythmogenic, (4) LV apical aneurysm, or (5) LV systolic dysfunction (EF less than 50%). It is a class IIb recommendation for an ICD if there is significant (greater than 15%) late gadolinium enhancement on cardiac MRI. In those who receive an ICD, antitachycardia pacing should be programmed to minimize shocks. The use of an ICD is contraindicated, though, if the purpose is simply to allow for the patient to play competitive sports.

Excision of part of the outflow myocardial septum (**myotomy–myomectomy**) by experienced surgeons is successful in patients with symptoms unresponsive to medical therapy. A few surgeons advocate mitral valve replacement, since this results in resolution of the gradient and prevents associated mitral regurgitation. In some cases, myomectomy has been combined with an Alfieri stitch on the mitral valve (a stitch that binds the midportion of the anterior and posterior mitral valve leaflets together). Rare cases of progression to LV dilation or patients with intractable symptoms can be considered for cardiac transplantation. Nonsurgical septal ablation can be performed by injection of alcohol into septal branches of the left coronary artery to create a controlled myocardial infarct in the regions of greatest wall thickness. It is now considered first-line therapy, if feasible, for those with LV outflow tract obstruction greater than 50 mm Hg who do not respond to medical therapy or who are not deemed surgical candidates.

In "burnt out" HCM, the medical therapy is similar to that of dilated cardiomyopathy. In those with refractory arrhythmias or heart failure, cardiac transplantation is an option.

Pregnancy results in an increased risk in patients with symptoms or outflow tract gradients of greater than 50 mm Hg. Genetic counseling is indicated before planned conception. In pregnant patients with HCM, continuation of beta-blocker therapy is recommended. For more details on the impact of HCM on sport, activity, and occupation (such as driving commercially or piloting an aircraft), the reader is referred to the discussions in the 2020 AHA/ACC guidelines.

When to Refer

Patients should be referred to a cardiologist to establish care, consider genetic testing, review the presence of any high-risk features, and discuss medications or the need for any intervention. This is particularly important if any symptoms are present.

Ommen SR. 2020 AHA/ACC guidelines for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary. Circulation. 2020;142:e533. [PMID: 33215938]

RESTRICTIVE CARDIOMYOPATHY

ESSENTIALS OF DIAGNOSIS

- Right heart failure tends to dominate over left heart failure.
- Pulmonary hypertension is present.
- Amyloidosis is the most common cause.
- Echocardiography is key to diagnosis.
- Radionuclide imaging or myocardial biopsy can confirm amyloid.

General Considerations

Restrictive cardiomyopathy is characterized by *impaired diastolic filling with reasonably preserved LV chamber size*. The condition is relatively uncommon, with the most frequent cause being amyloidosis. The diagnosis of **cardiac amyloidosis** has dramatically increased in the last few years since diagnostic testing has improved and there is an awareness of its prevalence. The prevalence of AL amyloid is approximately 12 cases per million, the prevalence of variant or hereditary ATTR amyloid is about 0.3 cases per million, and the prevalence of wild type ATTR amyloid is 155–191 cases per million. Many experts believe the actual prevalence of wild type ATTR is much higher. While light-chain amyloid proteins can be toxic to cardiomyocytes, they may also internalize into many cell types and this may explain some of the cardiac dysfunction observed. ATTR refers to transthyretin, a protein normally found in the liver that helps transport thyroid hormones and vitamin A. Wild type (normal) occurs more commonly in the elderly and in men, and previously was referred to as "senile systemic amyloidosis." Hereditary or variant ATTR is genetically transmitted, deposition occurs at an earlier age, and it has associated neurologic impact. TTR is a tetramer that can dissociate into four monomers and aggregate as amyloid fibrils. The differential diagnosis of a restrictive cardiomyopathy includes infiltrative disorders beside amyloidosis, such as sarcoidosis, Gaucher disease, and Hurler syndrome. Storage diseases such as hemochromatosis, Fabry disease, and glycogen storage diseases can also produce the picture. Noninfiltrative diseases, such as familial cardiomyopathy and pseudoxanthoma elasticum, can be implicated rarely, and other secondary causes include diabetes, systemic sclerosis (scleroderma), radiation, chemotherapy, CAD, and longstanding hypertension.

Clinical Findings

A. Symptoms and Signs

Restrictive cardiomyopathy must be distinguished from constrictive pericarditis (see Table 10–15). The key feature is that *ventricular interaction is accentuated with respiration in constrictive pericarditis* and that interaction is absent in restrictive cardiomyopathy. In addition, the pulmonary arterial pressure is invariably elevated in restrictive cardiomyopathy due to the high PCWP and is normal in uncomplicated constrictive pericarditis. Symptoms may include angina, syncope, stroke, and peripheral neuropathy. Periorbital purpura, a thickened tongue, and hepatomegaly are all suggestive physical findings of amyloidosis.

B. Diagnostic Studies

Conduction disturbances are frequently present. Low voltage on the ECG combined with ventricular hypertrophy on the echocardiogram is suggestive of disease. Technetium pyrophosphate imaging (bone scan imaging) can also identify amyloid deposition in the myocardium, and it has become the noninvasive imaging modality of choice for diagnosing transthyretin amyloidosis. With typical scintographic findings in patients without a monoclonal gammopathy, biopsy is no longer necessary for diagnosis. Cardiac MRI presents a distinctive pattern of diffuse hyperenhancement of the gadolinium image in amyloidosis and is a useful screening test. Late gadolinium hyperenhancement of a high degree suggests more extensive cardiac involvement. The echocardiogram reveals a small, thickened LV with bright myocardium (speckled), rapid early diastolic filling revealed by the mitral inflow Doppler, and biatrial enlargement. Characteristic longitudinal strain patterns may help identify cardiac amyloidosis. The LV chamber size is usually normal with a reduced LVEF. Atrial septal thickening may be evident and an amyloid variant that primarily affects the atria has been described. Rectal, abdominal fat, or gingival biopsies can confirm systemic involvement, but myocardial involvement may still be present if these are negative and requires endomyocardial

biopsy for the confirmation that cardiac amyloid is present. Demonstration of tissue infiltration on biopsy specimens using special stains followed by immunohistochemical studies and genetic testing are essential to define which specific protein is involved. TTR gene sequencing in patients in whom the TTR wild type or TTR mutant variant is suspected and mass spectroscopy on all tissue in question are recommended highly. BNP and NT-proBNP are traditionally elevated and have been used to help distinguish constrictive pericarditis from a restrictive cardiomyopathy.

Treatment

Treatment for AL amyloidosis includes alkylator-based chemotherapy or high-dose melphalan followed by autologous stem cell transplantation. In immunoglobin light chain amyloidosis, standard- or high-dose chemotherapy with stem cell rescue is often pursued. Treatment of ATTR amyloid is undergoing an evolution. Tafamidis helps prevent the misfolding of the TTR tetramer and is now approved for treatment. Patisiran is also available, and it inhibits both variant and wild type TTR production. For the variant TTR polyneuropathy, subcutaneous inotersen is available (it binds to TTR mRNA preventing transcription).

In acute heart failure, diuretics can help, but excessive diuresis can produce worsening kidney dysfunction. As with most patients with severe right heart failure, loop diuretics, thiazides, and aldosterone antagonists are all useful. Atrial thrombi are not uncommon, although the role of anticoagulation in amyloidosis remains ill defined. Digoxin may precipitate arrhythmias and should not be used. Beta-blockers help slow heart rates and improve filling by increasing diastolic time. Verapamil presumably works by improving myocardial relaxation and increasing diastolic filling time. Slow heart rates are desired to allow for increased diastolic filling time. ACE inhibition or angiotensin II receptor blockade may improve diastolic relaxation and filling at times and can be tried with caution if the systemic BP is adequate. Corticosteroids may be helpful in sarcoidosis, but they are more effective for conduction abnormalities in this disease than in heart failure.

When to Refer

All patients with the diagnosis of a restrictive cardiomyopathy should be referred to a cardiologist to decide etiology and plan appropriate treatment. Unexplained LVH with relatively preserved LVEF and symptoms of heart failure should raise the question of cardiac amyloid, particularly now that there is effective treatment available.

Kitaoka H et al; Japanese Circulation Society Joint Working Group. JCS 2020 guideline on diagnosis and treatment of cardiac amyloidosis. Circ J. 2020;84:1610. [PMID: 32830187]

Marques N et al. Specific therapy for transthyretin cardiac amyloidosis: a systematic literature review and evidence-based recommendations. J Am Heart Assoc. 2020;9:e016614. [PMID: 32969287]

RHEUMATIC FEVER

ESSENTIALS OF DIAGNOSIS

- More common in developing countries (100 cases/100,000 population) than in the United States (~2 cases/100,000 population).
- Peak incidence between ages 5 and 15 years.
- May involve mitral and other valves acutely, rarely leading to heart failure.

General Considerations

Rheumatic fever is a systemic immune process that is a sequela of a beta-hemolytic streptococcal infection of the pharynx. It is a major scourge in developing countries and responsible for 320,000 deaths in young people worldwide each year. Over 15 million people have evidence for rheumatic heart disease. Signs of **acute rheumatic fever** usually commence 2–3 weeks after infection but may appear as early as 1 week or as late as 5 weeks. The disease has become quite uncommon in the United States, except in immigrants. The peak incidence is between ages 5 and 15 years; rheumatic fever is rare before age 4 years or after age 40 years. Rheumatic carditis and valvulitis may be self-limited or may lead to slowly progressive valvular deformity. The characteristic lesion is a perivascular granulomatous reaction with valvulitis. The mitral valve is acutely attacked in 75–80% of cases, the aortic valve in 30% (but rarely as the sole valve involved), and the tricuspid and pulmonary valves in under 5% of cases.

The clinical profile of the infection includes carditis in 50–70% and arthritis in 35–66%, followed by chorea (10–30%, predominantly in girls) then subcutaneous nodules (0–10%) and erythema marginatum (in less than 6%). Echocardiography has been found to be superior to auscultation, and the 2015 guidelines introduced **subclinical carditis** to the Jones criteria to represent abnormal echocardiographic findings when auscultatory findings were either not present or not recognized.

Chronic rheumatic heart disease results from single or repeated attacks of rheumatic fever that produce rigidity and deformity of valve cusps, fusion of the commissures, or shortening and fusion of the chordae tendineae. Valvular stenosis or regurgitation results, and the two often coexist. In chronic rheumatic heart disease, the mitral valve alone is abnormal in 50–60% of cases; combined lesions of the aortic and mitral valves occur in 20%; pure aortic lesions are less common. Tricuspid involvement occurs in about 10% of cases, but only in association with mitral or aortic disease and is thought to be more common when recurrent infections have occurred. The pulmonary valve is rarely affected long term. A history of rheumatic fever is obtainable in only 60% of patients with rheumatic heart disease. While there has been progress against this disease, it remains a major cardiovascular problem in the poorest regions of the world.

Clinical Findings

The presence of two major criteria—or one major and two minor criteria—establishes the diagnosis. While India, New Zealand, and Australia have all published revised guidelines since 2001, the 2015 recommendations have revised the Jones criteria (Table 10–16) in a scientific statement from the AHA where subclinical carditis is now recognized with the advent of echocardiography. The revised criteria also recognize that a lower threshold should be used to diagnosis acute rheumatic fever in high-risk populations.

A. Major Criteria

1. Carditis—Carditis is most likely to be evident in children and adolescents. Any of the following suggests the presence of carditis: (1) pericarditis; (2) cardiomegaly, detected by physical signs, radiography, or echocardiography; (3) heart failure, right- or left-sided—the former perhaps more prominent in children, with painful liver engorgement due to tricuspid regurgitation; and (4) mitral or aortic regurgitation murmurs, indicative of dilation of a valve ring with or without associated valvulitis or morphologic findings on echocardiography of rheumatic valvulitis. The Carey–Coombs short mid-diastolic mitral murmur may be present due to inflammation of the mitral valve. It is a class I (LOE B) indication to perform echocardiography/Doppler studies on all cases of suspected or confirmed acute rheumatic fever.

2. Erythema marginatum and subcutaneous nodules—Erythema marginatum begins as rapidly enlarging macules that may be less notable on black skin and that assume the shape of rings or crescents with clear centers. They may be raised, confluent, and either transient or persistent and usually on the trunk or proximal extremities. Subcutaneous nodules are uncommon except in children. They are small (2 cm or less in diameter), firm, and nontender and are attached to fascia or tendon sheaths over bony prominences. They persist for days or weeks, are recurrent, and are indistinguishable from rheumatoid nodules. Neither the rash nor nodules ever occur as the sole manifestation of acute rheumatic fever.

3. Sydenham chorea—This is the most definitive manifestation of acute rheumatic fever. Defined as involuntary choreoathetoid movements primarily of the face, tongue, and upper extremities, Sydenham chorea may be the sole manifestation of rheumatic fever. Girls are more frequently affected than boys, and occurrence in adults is rare.

4. Polyarthritis—This is a migratory polyarthritis that involves the large joints sequentially. In adults and in certain moderate- to high-risk populations, only a single joint may be affected. The arthritis lasts 1–5 weeks and subsides without residual deformity. Prompt response of arthritis to therapeutic doses of salicylates or nonsteroidal agents is characteristic.

B. Minor Criteria

These include fever, polyarthralgia, reversible prolongation of the PR interval, and an elevated ESR or CRP. A lower threshold is set for patients at high risk (Table 10–16). The 2015 guidelines stipulate that evidence for a preceding

Table 10–16. The 2015 revised Jones criteria.[1]

Population	Criteria	
	Major	Minor
Low risk	Carditis (clinical or subclinical)	Polyarthralgia
	Arthritis (polyarthritis only)	Fever (≥ 38.5°C)
	Chorea	ESR ≥ 60 mm/hour or CRP ≥ 3.0 mg/dL (or both)
	Erythema marginatum	Prolonged PR interval (unless carditis is major criterion)
	Subcutaneous nodules	
Moderate and high risk	Carditis (clinical or subclinical)	Monoarthralgia
	Arthritis (monoarthritis, polyarthritis, polyarthralgia)	Fever (≥ 38°C)
	Chorea	ESR ≥ 30 mm/hour or CRP ≥ 3.0 mg/dL (or both)
	Erythema marginatum	Prolonged PR interval (unless carditis is a major criterion)
	Subcutaneous nodules	

[1]For all patients with evidence of preceding group A streptococcal pharyngitis: initial acute rheumatic fever can be diagnosed when 2 major criteria or 1 major plus 2 minor criteria are met. Recurrent acute rheumatic fever can be diagnosed when 2 major or 1 major plus 2 minor or 3 minor criteria are met. Reprinted with permission Circulation. 2015;131:1806–1818 ©2015 American Heart Association, Inc.

streptococcal infection can be defined by an increase or rising anti-streptolysin O titer or streptococcal antibodies (anti-DNAase B), a positive throat culture for group A beta-hemolytic streptococcal or a positive rapid group A streptococcal carbohydrate antigen test in a child with a high pretest probability of streptococcal pharyngitis.

Treatment

A. General Measures

The patient should be kept at strict bed rest until the temperature returns to normal (without the use of antipyretic medications) and the ESR, plus the resting pulse rate, and the ECG have all returned to baseline.

B. Medical Measures

1. Salicylates—The salicylates markedly reduce fever and relieve joint pain and swelling. They have no effect on the natural course of the disease. Adults may require large doses of aspirin, 0.6–0.9 g every 4 hours; children are treated with lower doses.

2. Penicillin—Penicillin (benzathine penicillin, 1.2 million units intramuscularly once, or procaine penicillin, 600,000 units intramuscularly daily for 10 days) is used to eradicate streptococcal infection if present. Erythromycin may be substituted (40 mg/kg/day).

3. Corticosteroids—There is no proof that cardiac damage is prevented or minimized by corticosteroids. A short course of corticosteroids (prednisone, 40–60 mg orally daily, with tapering over 2 weeks) usually causes rapid improvement of the joint symptoms and is indicated when response to salicylates has been inadequate.

Prevention of Recurrent Rheumatic Fever

Improvements in socioeconomic conditions and public health are critical to reducing bouts of rheumatic fever. The initial episode of rheumatic fever can usually be prevented by early treatment of streptococcal pharyngitis with penicillin (see Chapter 33). Prevention of recurrent episodes of rheumatic fever is critical. Recurrences of rheumatic fever are most common in patients who have had carditis during their initial episode and in children, 20% of whom will have a second episode within 5 years. The preferred method of prophylaxis is with benzathine penicillin G, 1.2 million units intramuscularly every 4 weeks. Oral penicillin (250 mg twice daily) is less reliable.

If the patient is allergic to penicillin, sulfadiazine (or sulfisoxazole), 1 g daily, or erythromycin, 250 mg orally twice daily, may be substituted. The macrolide azithromycin is similarly effective against group A streptococcal infection. If the patient has not had an immediate hypersensitivity (anaphylactic-type) reaction to penicillin, then cephalosporin may also be used.

Recurrences are uncommon after 5 years following the first episode and in patients over 21 years of age. Prophylaxis is usually discontinued after these times except in groups with a high risk of streptococcal infection—parents or teachers of young children, nurses, military recruits, etc. Secondary prevention of rheumatic fever depends on whether carditis has occurred. Current guidelines suggest that if there is no evidence for carditis, preventive therapy can be stopped at age 21 years. If carditis has occurred but there is no residual valvular disease, it can be stopped at 10 years after the acute rheumatic fever episode. If carditis has occurred with residual valvular involvement, it should be continued for 10 years after the last episode or until age 40 years if the patient is in a situation in which reexposure would be expected.

Prognosis

Initial episodes of rheumatic fever may last months in children and weeks in adults. The immediate mortality rate is 1–2%. Persistent rheumatic carditis with cardiomegaly, heart failure, and pericarditis implies a poor prognosis; 30% of children thus affected die within 10 years after the initial attack. After 10 years, two-thirds of patients will have detectable valvular abnormalities (usually thickened valves with limited mobility), but significant symptomatic valvular heart disease or persistent cardiomyopathy occurs in less than 10% of patients with a single episode. In developing countries, acute rheumatic fever occurs earlier in life and recurs more frequently; thus, the evolution to chronic valvular disease is both accelerated and more severe.

Dooley LM et al. Rheumatic heart disease: a review of the current status of global research activity. Autoimmun Rev. 2021;20:102740. [PMID: 33333234]

DISEASES OF THE PERICARDIUM

ACUTE INFLAMMATORY PERICARDITIS

ESSENTIALS OF DIAGNOSIS

- Anterior pleuritic chest pain that is worse supine than upright.
- Pericardial rub.
- Fever common.
- ESR or inflammatory CRP usually elevated.
- ECG reveals diffuse ST-segment elevation with associated PR depression.

General Considerations

Acute (less than 2 weeks) inflammation of the pericardium may be infectious in origin or may be due to systemic diseases (autoimmune syndromes, uremia), neoplasm, radiation, drug toxicity, hemopericardium, postcardiac surgery, or contiguous inflammatory processes in the myocardium or lung. In many of these conditions, the pathologic process involves both the pericardium and the myocardium. Overall pericarditis accounts for 0.2% of hospital admissions and about 5% of patients with nonischemic chest pain

seen in the emergency department. The ESC in 2015 proposed four categories of pericarditis: acute, incessant, current, and chronic. Each category has its own diagnostic criteria. In **acute pericarditis,** there are four criteria: (1) pericardial chest pain, (2) pericardial rub, (3) new widespread ST-elevation or PR depression, and (4) new or worsening pericardial effusion. To establish the diagnosis of acute pericarditis, at least two of these four criteria must be present. **Incessant pericarditis** is defined by its duration; it lasts longer than 4–6 weeks but less than 3 months without remission. **Recurrent pericarditis** can be diagnosed in a patient with one reported episode of pericarditis who has been symptom free for at least 4–6 weeks. Finally, **chronic pericarditis** is diagnosed when it persists for more than 3 months.

Viral infections (especially infections with coxsackieviruses and echoviruses but also influenza, Epstein-Barr, varicella, hepatitis, mumps, and HIV viruses) are the most common cause of acute pericarditis and probably are responsible for many cases classified as idiopathic. COVID-19 has been associated with both acute pericarditis and even cardiac tamponade. Males—usually under age 50 years—are most commonly affected. The differential diagnosis primarily requires exclusion of acute MI. **Tuberculous pericarditis** is rare in developed countries but remains common in certain areas of the world. It results from direct lymphatic or hematogenous spread; clinical pulmonary involvement may be absent or minor, although associated pleural effusions are common. **Bacterial pericarditis** is equally rare and usually results from direct extension from pulmonary infections. Pneumococci, though, can cause a primary pericardial infection. *Borrelia burgdorferi,* the organism responsible for Lyme disease, can also cause myopericarditis (and occasionally heart block). **Uremic pericarditis** is a common complication of CKD. The pathogenesis is uncertain; it occurs both with untreated uremia and in otherwise stable dialysis patients. Spread of adjacent lung cancer as well as invasion by breast cancer, renal cell carcinoma, Hodgkin disease, and lymphomas are the most common **neoplastic processes** involving the pericardium and have become the most frequent causes of pericardial tamponade in many countries. Pericarditis may occur 2–5 days after infarction due to an inflammatory reaction to transmural myocardial necrosis **(post-MI** or **postcardiotomy pericarditis [Dressler syndrome]). Radiation** can initiate a fibrinous and fibrotic process in the pericardium, presenting as subacute pericarditis or constriction. Radiation pericarditis usually follows treatments of more than 4000 cGy delivered to ports including more than 30% of the heart.

Other causes of pericarditis include **connective tissue diseases,** such as SLE and rheumatoid arthritis, **drug-induced pericarditis** (minoxidil, penicillins, clozapine), and **myxedema.** In addition, pericarditis may result from **pericardial injury** from invasive cardiac procedures (such as cardiac pacemaker and defibrillator perforation and intracardiac ablation, especially atrial fibrillation ablation), and the implantation of intracardiac devices (such as ASD occluder devices).

Pericarditis and myocarditis may coexist in 20–30% of patients. Myocarditis is often suspected when there is an elevation of serum troponins, although there are no data that suggest troponin elevations are associated with a poor prognosis.

Clinical Findings

A. Symptoms and Signs

The presentation and course of inflammatory pericarditis depend on its cause, but most syndromes have associated chest pain, which is usually pleuritic and postural (relieved by sitting). The pain is substernal but may radiate to the neck, shoulders, back, or epigastrium. Dyspnea may also be present and the patient is often febrile. A pericardial **friction rub** is characteristic, with or without evidence of fluid accumulation or constriction. The presentation of tuberculous pericarditis tends to be subacute, but nonspecific symptoms (fever, night sweats, fatigue) may be present for days to months. Pericardial involvement develops in 1–8% of patients with pulmonary tuberculosis. Symptoms and signs of bacterial pericarditis are similar to those of other types of inflammatory pericarditis, but patients appear toxic and are often critically ill. Uremic pericarditis can present with or without symptoms; fever is absent. Often neoplastic pericarditis is painless, and the presenting symptoms relate to hemodynamic compromise or the primary disease. At times the pericardial effusion is very large, consistent with its chronic nature. Post-MI or postcardiotomy pericarditis (Dressler syndrome) usually presents as a recurrence of pain with pleural-pericardial features. A rub is often audible, and repolarization changes on the ECG may be confused with ischemia. Large effusions are uncommon, and spontaneous resolution usually occurs in a few days. Dressler syndrome occurs days to weeks to several months after MI or open heart surgery, may be recurrent, and probably represents an autoimmune syndrome. Patients present with typical pain, fever, malaise, and leukocytosis. Rarely, other symptoms of an autoimmune disorder, such as joint pain and fever, may occur. Tamponade is rare with Dressler syndrome after MI but not when it occurs postoperatively. The clinical onset of radiation pericarditis is usually within the first year but may be delayed for many years; often a full decade or more may pass before constriction becomes evident.

B. Laboratory Findings and Diagnostic Studies

The diagnosis of viral pericarditis is usually clinical, and leukocytosis is often present. Rising viral titers in paired sera may be obtained for confirmation but are rarely done. Cardiac enzymes may be slightly elevated, reflecting an epicardial myocarditis component. The echocardiogram is often normal or reveals only a trivial amount of extra fluid during the acute inflammatory process. The diagnosis of tuberculous pericarditis can be inferred if acid-fast bacilli are found elsewhere. The tuberculous pericardial effusions are usually small or moderate but may be large when chronic. The yield of mycobacterial organisms by pericardiocentesis is low; pericardial biopsy has a higher yield but may also be negative, and pericardiectomy may be required. If bacterial pericarditis is suspected on clinical grounds, diagnostic pericardiocentesis can be confirmatory. In uremic patients

not on dialysis, the incidence of pericarditis correlates roughly with the level of BUN and creatinine. The pericardium is characteristically "shaggy" in uremic pericarditis, and the effusion is hemorrhagic and exudative. The diagnosis of neoplastic pericarditis can occasionally be made by cytologic examination of the effusion or by pericardial biopsy, but it may be difficult to establish clinically if the patient has received mediastinal radiation within the previous year. Neoplastic pericardial effusions develop over a long period of time and may become quite huge (more than 2 L). The ESR is high in post-MI or postcardiotomy pericarditis and can help confirm the diagnosis. Large pericardial effusions and accompanying pleural effusions are frequent. Myxedema pericardial effusions due to hypothyroidism usually are characterized by the presence of cholesterol crystals within the fluid.

C. Other Studies

The ECG usually shows generalized ST and T wave changes and may manifest a characteristic progression beginning with diffuse ST elevation, followed by a return to baseline and then to T-wave inversion. Atrial injury is often present and manifested by PR depression, especially in the limb leads. The chest radiograph is frequently normal but may show cardiac enlargement (if pericardial fluid is present), as well as signs of related pulmonary disease. Mass lesions and enlarged lymph nodes may suggest a neoplastic process. About 60% of patients have a pericardial effusion (usually mild) detectable by echocardiography. MRI and CT scan can visualize neighboring tumor in neoplastic pericarditis. A screening chest CT or MRI is often recommended to ensure there are no extracardiac diseases contiguous to the pericardium. A consensus statement from the American Society of Echocardiography proposes adding an elevated CRP and late gadolinium enhancement of the pericardium to confirmatory criteria for the diagnosis of pericarditis. There are data that the degree of quantitative delayed enhancement of the pericardium is associated with a higher rate of recurrent pericarditis. PET scanning can also be used to help define pericardial inflammation.

Treatment

For acute pericarditis, experts suggest a restriction in activity until symptom resolution. For athletes, the duration of exercise restriction should be until resolution of symptoms and normalization of all laboratory tests (generally 3 months). The 2015 ESC guidelines recommend aspirin 750–1000 mg every 8 hours for 1–2 weeks with a taper by decreasing the dose 250–500 mg every 1–2 weeks or ibuprofen 600 mg every 8 hours for 1–2 weeks with a taper by decreasing the dose by 200–400 mg every 1–2 weeks. Gastroprotection should be included. Studies support initial treatment of the acute episode with colchicine to prevent recurrences. Colchicine should be added to the NSAID at 0.5–0.6 mg once (for patients less than 70 kg) or twice (for patients more than 70 kg) daily and continued for at least 3 months. Tapering of colchicine is not mandatory; however, in the last week of treatment, the dosage can be reduced every other day for patients less than 70 kg or once a day for those more than 70 kg. Aspirin and colchicine should be used instead of NSAIDs in post-MI pericarditis (Dressler syndrome), since NSAIDs and corticosteroids may have an adverse effect on myocardial healing. Aspirin in doses of 750–1000 mg three times daily for 1–2 weeks plus 3 months of colchicine is the recommended treatment for Dressler syndrome. Despite initial treatment, recurrence has been reported in about 30%.

Colchicine should be used for at least 6 months as therapy in all refractory cases and in recurrent pericarditis. At times a longer duration of therapy is required. The CRP is used to assess the effectiveness of treatment, and once it is normalized, tapering is initiated. Indomethacin in doses of 25–50 mg every 8 hours can also be considered in recurrent pericarditis in place of ibuprofen. Systemic corticosteroids can be added in patients with severe symptoms, in refractory cases, or in patients with immune-mediated etiologies, but such therapy may entail a higher risk of recurrence and may actually prolong the illness. Colchicine is recommended in addition to corticosteroids, again for at least 3 months, to help prevent recurrences. Prednisone in doses of 0.25–0.5 mg/kg/day orally is generally suggested with tapering over a 4- to 6-week period. Recent studies have confirmed the advantage of adding anakinra, an interleukin-1 receptor antagonist, for the treatment of recurrent pericarditis, especially for corticosteroid-dependent and colchicine-resistant pericarditis.

As a rule, symptoms subside in several days to weeks. The major early complication is **tamponade,** which occurs in less than 5% of patients. There may be recurrences in the first few weeks or months. Rarely, when colchicine therapy alone fails or cannot be tolerated (usually due to GI symptoms), the pericarditis may require more significant immunosuppression, such as cyclophosphamide, azathioprine, intravenous human immunoglobulins, interleukin-1 receptor antagonists (anakinra), or methotrexate. If colchicine plus more significant immunosuppression fails, surgical pericardial stripping may be considered in recurrent cases even without clinical evidence for constrictive pericarditis.

Standard antituberculous medication therapy is usually successful for tuberculous pericarditis (see Chapter 9), but constrictive pericarditis can occur. Uremic pericarditis usually resolves with the institution of—or with more aggressive—dialysis. Tamponade is fairly common, and partial pericardiectomy (**pericardial window**) may be necessary. Whereas anti-inflammatory agents may relieve the pain and fever associated with uremic pericarditis, indomethacin and systemic corticosteroids do not affect its natural history. The prognosis with neoplastic effusion is poor, with only a small minority surviving 1 year. If it is compromising the clinical comfort of the patient, the effusion is initially drained percutaneously. Attempts at balloon pericardiotomy have been abandoned because outcomes were not more effective than simple drainage. A pericardial window, either by a subxiphoid approach or via video-assisted thoracic surgery, allows for partial pericardiectomy. Installation of chemotherapeutic agents or tetracycline may be used to reduce the recurrence rate. Symptomatic therapy is the initial approach to radiation pericarditis, but recurrent effusions and constriction often require surgery.

Prognosis

There are data that patients with acute pericarditis and any of the following criteria have the poorest prognosis: fever higher than 38°C, subacute onset, large effusion with or without tamponade, lack of response to anti-inflammatory medication after 1 week, myopericarditis, traumatic pericarditis, and those on oral anticoagulation. About 15% of patients have at least one of these high-risk findings.

When to Refer

Patients who do not respond initially to conservative management, who have recurrences, or who appear to be developing constrictive pericarditis should be referred to a cardiologist for further assessment.

Imazio M et al. Anakinra for corticosteroid-dependent and colchicine-resistant pericarditis. The IRAP (International Registry of Anakinra for Pericarditis) study. Eur J Prev Cardiol 2020;27:956. [PMID: 31610707]

PERICARDIAL EFFUSION & TAMPONADE

ESSENTIALS OF DIAGNOSIS

Pericardial effusion

- Clinical impact determined by the speed of accumulation.
- May or may not cause pain.

Tamponade

- Tachycardia with an elevated JVP and either hypotension or a paradoxical pulse.
- Low voltage or electrical alternans on ECG.
- Echocardiography is diagnostic.

Pericardial effusion can develop during any of the acute pericarditis processes. Because the pericardium covers the ascending aorta and arch, aortic dissection and/or rupture can lead to tamponade as well. The *speed of accumulation* determines the physiologic importance of the effusion. Because of pericardial stretch, effusions larger than 1000 mL that develop slowly may produce no hemodynamic effects. Conversely, smaller effusions that appear rapidly can cause tamponade due to the curvilinear relationship between the volume of fluid and the intrapericardial pressure. Tamponade is characterized by elevated intrapericardial pressure (greater than 15 mm Hg), which restricts venous return and ventricular filling. As a result, the stroke volume and arterial pulse pressure fall, and the heart rate and venous pressure rise. Shock and death may result.

Clinical Findings

A. Symptoms and Signs

Pericardial effusions may be associated with pain if they occur as part of an acute inflammatory process or may be painless, as is often the case with neoplastic or uremic effusion. Dyspnea and cough are common, especially with tamponade. Cardiac tamponade can be a life-threatening syndrome evidenced by tachycardia, hypotension, pulsus paradoxicus, raised JVP, muffled heart sounds, and decreased ECG voltage or electrical alternans. Other symptoms may result from the primary disease. The prognosis is a function of the cause. Large idiopathic chronic effusions (over 3 months) have a 30–35% risk of progression to cardiac tamponade.

A pericardial friction rub may be present even with large effusions. In cardiac tamponade, tachycardia, tachypnea, a narrow pulse pressure, and a relatively preserved systolic pressure are characteristic. **Pulsus paradoxus** is defined as a decline of greater than 10 mm Hg in systolic pressure during inspiration. Since the RV and LV share the same pericardium, when there is significant pericardial effusion, as the RV enlarges with inspiratory filling, septal motion toward the LV chamber reduces LV filling and results in an accentuated drop in the stroke volume and systemic BP with inspiration (the paradoxical pulse). Central venous pressure is elevated and, since the intrapericardial, and thus intracardiac, pressures are high even at the initiation of diastole, there is no evident *y* descent in the RA, RV, or LV hemodynamic tracings because the pericardial pressure prevents early ventricular filling. This differs from constriction where most of the initial filling of the RV and LV occurs during early diastole (rapid *y* descent), and it is only in mid to late diastole that the ventricles can no longer fill. In tamponade, ventricular filling is inhibited throughout diastole. Edema or ascites are rarely present in tamponade; these signs favor a more chronic process.

B. Laboratory Findings

Laboratory tests tend to reflect the underlying processes (see causes of pericarditis under General Considerations above).

C. Diagnostic Studies

Chest radiograph can suggest chronic effusion by an enlarged cardiac silhouette with a globular configuration but may appear normal in acute situations. The ECG often reveals nonspecific T wave changes and reduced QRS voltage. **Electrical alternans** is present only occasionally but is pathognomonic and is believed to be due to the heart swinging within the large effusion. Echocardiography is the primary method for demonstrating pericardial effusion and is quite sensitive. If tamponade is present, the high intrapericardial pressure may collapse lower pressure cardiac structures, such as the RA and RV. Cardiac CT and MRI also demonstrate pericardial fluid, pericardial thickening, and any associated contiguous lesions within the chest. Diagnostic pericardiocentesis or biopsy may be indicated for microbiologic and cytologic studies; a pericardial biopsy may be performed relatively simply through a small subxiphoid incision or by use of a video-assisted thoracoscopic surgical procedure. Unfortunately, the quality of the pericardial fluid itself rarely leads to a diagnosis, and any type of fluid (serous, serosanguinous, bloody, etc) can be seen in most diseases. Pericardial fluid analysis is most useful in excluding a bacterial cause and is

occasionally helpful in malignancies. Effusions due to hypothyroidism or lymphatic obstruction may contain cholesterol or be chylous in nature, respectively.

Treatment

Small effusions can be followed clinically by careful observations of the JVP and by testing for a change in the paradoxical pulse. The most common cause of a paradoxical pulse is severe pulmonary disease, especially asthma, where marked changes in intrapleural pressures occur with inspiration and expiration. Serial echocardiograms are indicated if no intervention is immediately contemplated. Vasodilators and diuretics should be avoided. **When tamponade is present, urgent pericardiocentesis or cardiac surgery is required.** Because the pressure–volume relationship in the pericardial fluid is curvilinear and upsloping, removal of even a small amount of fluid often produces a dramatic fall in the intrapericardial pressure and immediate hemodynamic benefit; but complete drainage with a catheter is preferable. Continued or repeat drainage may be indicated, especially in malignant effusions. Pericardial windows via video-assisted thoracoscopy have been particularly effective in preventing recurrences when the underlying cause of the effusion continues to be present and are more effective than needle pericardiocentesis, subxiphoid surgical windows, or percutaneous balloon pericardiotomy. Effusions related to recurrent inflammatory pericarditis can be treated as noted above (see Acute Inflammatory Pericarditis). The presence of pericardial fluid in patients with pulmonary hypertension is a poor prognostic sign.

When to Refer

- Any unexplained pericardial effusion should be referred to a cardiologist.
- Trivial pericardial effusions are common, especially in heart failure, and need not be referred unless symptoms of pericarditis are evident.
- Hypotension or a paradoxical pulse suggesting the pericardial effusion is hemodynamically compromising the patient is a medical emergency and requires immediate drainage.
- Any echocardiographic signs of tamponade.

CONSTRICTIVE PERICARDITIS

ESSENTIALS OF DIAGNOSIS

- Clinical evidence of right heart failure.
- No fall or an elevation of the JVP with inspiration (Kussmaul sign).
- Echocardiographic evidence for septal bounce and reduced mitral inflow velocities with inspiration.
- At times may be difficult to differentiate from restrictive cardiomyopathy.
- Cardiac catheterization may be necessary when clinical and echocardiographic features are equivocal.

General Considerations

Pericardial inflammation can lead to a thickened, fibrotic, adherent pericardium that restricts diastolic filling and produces chronically elevated venous pressures. In the past, tuberculosis was the most common cause of constrictive pericarditis, but while it remains so in underdeveloped countries, it is rare now in the rest of the world. Constrictive pericarditis rarely occurs following recurrent pericarditis. The risk of constrictive pericarditis due to viral or idiopathic pericarditis is less than 1%. Its occurrence increases following immune-mediated or neoplastic pericarditis (2–5%) and is highest after purulent bacterial pericarditis (20–30%). Other causes include post cardiac surgery, radiation therapy, and connective tissue disorders. A small number of cases are drug-induced or secondary to trauma, asbestosis, sarcoidosis, or uremia. At times, both pericardial tamponade and constrictive pericarditis may coexist, a condition referred to as **effusive-constrictive pericarditis**. The only definitive way to diagnose this condition is to reveal the underlying constrictive physiology once the pericardial fluid is drained. The differentiation of constrictive pericarditis from a restrictive cardiomyopathy may require cardiac catheterization and the utilization of all available noninvasive imaging methods.

Clinical Findings

A. Symptoms and Signs

The principal symptoms are slowly progressive dyspnea, fatigue, and weakness. Chronic edema, hepatic congestion, and ascites are usually present. Ascites often seems out of proportion to the degree of peripheral edema. The examination reveals these signs and a characteristically elevated jugular venous pressure with a rapid *y* descent. This can be detected at bedside by careful observation of the jugular pulse and noting an apparent increased pulse wave at the end of ventricular systole (due to the relative accentuation of the *v* wave by the rapid *y* descent). **Kussmaul sign**—a failure of the JVP to fall with inspiration—is also a frequent finding. The apex may actually retract with systole and a pericardial "knock" may be heard in early diastole. Pulsus paradoxus is unusual. Atrial fibrillation is common.

B. Diagnostic Studies

At times, constrictive pericarditis is extremely difficult to differentiate from restrictive cardiomyopathy and the two may coexist. When unclear, the use of both noninvasive testing and cardiac catheterization is required to sort out the difference.

1. Radiographic findings—The chest radiograph may show normal heart size or cardiomegaly. Pericardial calcification is best seen on the lateral view and is uncommon. It rarely involves the LV apex, and finding of calcification at the LV apex is more consistent with LV aneurysm.

2. Echocardiography—Echocardiography rarely demonstrates a thickened pericardium. A **septal "bounce"** reflecting the rapid early filling is common, though. RV/LV interaction may be demonstrated by an inspiratory

reduction in the mitral inflow Doppler pattern of greater than 25%, much as in tamponade. Usually the initial mitral inflow into the LV is very rapid, and this can be demonstrated as well by the Doppler inflow (E wave) pattern. Other echocardiographic features, such as the ratio of the medial and lateral mitral annular motion (e' velocity), the respiration-related septal shift, and hepatic vein expiratory diastolic reversal ratio, also suggest constrictive physiology.

3. Cardiac CT and MRI—These imaging tests are only occasionally helpful. Pericardial thickening of more than 4 mm must be present to establish the diagnosis, but no pericardial thickening is demonstrable in 20–25% of patients with constrictive pericarditis. Some MRI techniques demonstrate the septal bounce and can provide further evidence for ventricular interaction.

4. Cardiac catheterization—This procedure is often confirmatory or can be diagnostic in difficult cases where the echocardiographic features are unclear or mixed. As a generality, the pulmonary pressure is low in constriction (as opposed to restrictive cardiomyopathy). In constrictive pericarditis, because of the need to demonstrate RV/LV interaction, cardiac catheterization should include simultaneous measurement of both the LV and RV pressure tracings with inspiration and expiration. This interaction can be demonstrated by cardiac MRI. Hemodynamically, patients with constriction have equalization of end-diastolic pressures throughout their cardiac chambers, there is rapid early filling then an abrupt increase in diastolic pressure (**"square-root" sign**), the RV end-diastolic pressure is more than one-third the systolic pressure, simultaneous measurements of RV and LV systolic pressure reveal a discordance with inspiration (the RV rises as the LV falls), and there is usually a Kussmaul sign (failure of the RA pressure to fall with inspiration). In restrictive cardiomyopathy, there is concordance of RV and LV systolic pressures with inspiration.

Treatment

Therapy should be aimed at the specific etiology initially. If there is laboratory evidence of ongoing inflammation, then anti-inflammatory medications may have a role. Once the hemodynamics are evident, the mainstay of treatment is diuresis. As in other disorders of right heart failure, the diuresis should be aggressive, using loop diuretics (oral torsemide or bumetanide if bowel edema is suspected or intravenous furosemide), thiazides, and aldosterone antagonists (especially in the presence of ascites and liver congestion). Surgical pericardiectomy should be recommended when diuretics are unable to control symptoms. Pericardiectomy removes only the pericardium between the phrenic nerve pathways, however, and most patients still require diuretics after the procedure, though symptoms are usually dramatically improved. Morbidity and mortality after pericardiectomy are high (up to 15%) and are greatest in those with the most disability prior to the procedure. Poor prognostic predictors include prior radiation, kidney dysfunction, higher pulmonary systolic pressures, abnormal LV systolic function, a lower serum sodium level, liver dysfunction, and older age. Pericardial calcium has no impact on survival.

When to Refer

If the diagnosis of constrictive pericarditis is unclear or the symptoms of fluid retention resist medical therapy, then referral to a cardiologist is warranted to both establish the diagnosis and recommend therapy.

Anasari-Gilani K et al. Multimodality approach to the diagnosis and management of constrictive pericarditis. Echocardiography. 2020;30:632. [PMID: 32240548]

Goldstein JA et al. Hemodynamics of constrictive pericarditis and restrictive cardiomyopathy. Catheter Cardiovasc Interv. 2020;95:1240. [PMID: 31904891]

PULMONARY HYPERTENSION

ESSENTIALS OF DIAGNOSIS

- Mean PA pressure ≥ 25 mm Hg.
- Dyspnea and often cyanosis.
- Enlarged pulmonary arteries on chest radiograph.
- Elevated JVP and RV heave.
- Echocardiography is often diagnostic.

General Considerations

The normal pulmonary bed offers about one-tenth as much resistance to blood flow as the systemic arterial system. Based on the 2019 Sixth World Symposium on Pulmonary Hypertension, the definition of pulmonary hypertension was changed. It was defined by a mean PA pressure of 20 mm Hg with a pulmonary vascular resistance of greater than or equal to 3 Wood units. Three categories were then defined:

1. Precapillary pulmonary hypertension: mean pulmonary artery pressure greater than 20 mm Hg, PVR greater than or equal to 3.0 Wood units, PCWP less than or equal to 15 mm Hg
2. Isolated post-capillary pulmonary hypertension: mean pulmonary artery pressure greater than 20 mm Hg, PVR less than 3.0 Wood units, PCWP greater than 15 mm Hg
3. Combined pre- and post-pulmonary hypertension: mean pulmonary artery pressure greater than 20 mm Hg, PVR greater than or equal to 3.0 Wood units, PCWP greater than 15 mm Hg

The clinical classification of pulmonary hypertension by the Sixth World Symposium on Pulmonary Hypertension is outlined in Table 10–17.

Group I includes **pulmonary arterial hypertension (PAH)** related to an underlying pulmonary vasculopathy. It includes the former "primary pulmonary hypertension" under the term "idiopathic pulmonary hypertension" and is defined as pulmonary hypertension and elevated PVR in the absence of other disease of the lungs or heart. Its cause

Table 10–17. Updated classification of pulmonary hypertension (PH).

Pulmonary arterial hypertension (PAH)
Idiopathic PAH
Heritable PAH
Drug- and toxin-induced PAH
PAH associated with connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis
PAH long-term responders to calcium channel blockers
PAH with overt features of venous/capillaries (PVOD/PCH) involvement
Persistent PH of the newborn syndrome
PH due to left heart disease
Due to heart failure with preserved LVEF
Due to heart failure with reduced LVEF
Valvular heart disease
Congenital/acquired cardiovascular conditions leading to post-capillary pulmonary hypertension
PH due to lung diseases or hypoxia (or both)
Obstructive lung disease
Restrictive lung disease
Other lung disease with mixed obstructive/restrictive pattern
Hypoxia without lung disease
Developmental lung disorders
PH due to pulmonary artery obstructions
Chronic thromboembolic pulmonary hypertension
Other pulmonary artery obstructions
PH with unclear or multifactorial mechanisms
Hematologic disorders
Systemic and metabolic disorders
Others
Complex congenital heart disease

PVOD/PCH, pulmonary veno-occlusive disease/ pulmonary capillary hemangiomatosis.

is unknown. About 6–10% have heritable PAH. Drug and toxic pulmonary hypertension have been described as associated with the use of anorexigenic agents that increase serotonin release and block its uptake. These include aminorex fumarate, fenfluramine, and dexfenfluramine. In some cases, there is epidemiologic linkage to ingestion of rapeseed oil or L-tryptophan and use of recreational drugs, such as amphetamines and cocaine. Pulmonary hypertension associated with connective tissue disease includes cases associated with systemic sclerosis—up to 8–12% of patients with systemic sclerosis may be affected. Pulmonary hypertension has also been associated with HIV infection, portal hypertension, congenital heart disease (Eisenmenger syndrome), schistosomiasis, and chronic hemolytic anemia (eg, sickle cell anemia). In rare instances, obstruction of the pulmonary venous circulation may occur (pulmonary veno-occlusive disease and capillary hemangiomatosis).

Group II includes all cases related to left heart disease. **Group III** includes cases due to parenchymal lung disease, impaired control of breathing, or living at high altitude. This group encompasses those with idiopathic pulmonary fibrosis and COPD. **Group IV** represents patients with chronic thromboembolic disease or other pulmonary artery obstruction. **Group V** includes multifactorial causes such as hematologic, systemic, and metabolic disorders.

Clinical Findings

A. Symptoms and Signs

Common to all is exertional dyspnea, chest pain, fatigue, and lightheadedness as early symptoms; later symptoms include syncope, abdominal distention, ascites, and peripheral edema as RV function worsens. Chronic lung disease, especially sleep apnea, often is overlooked as a cause for pulmonary hypertension as is chronic thromboembolic disease. Patients with idiopathic pulmonary hypertension are characteristically young women who have evidence of right heart failure that is usually progressive, leading to death in 2–8 years without therapy. This is a decidedly different prognosis than patients with Eisenmenger physiology due to a left-to-right shunt; 40% of patients with Eisenmenger physiology are alive 25 years after the diagnosis has been made. Patients have manifestations of low cardiac output, with weakness and fatigue, as well as edema and ascites as right heart failure advances. Peripheral cyanosis is present, and syncope on effort may occur.

B. Diagnostic Studies

The ESC and European Respiratory Society updated guidelines for the diagnosis and treatment of pulmonary hypertension in 2019. All patients with a high risk for PAH should undergo *confirmatory right heart catheterization*.

The laboratory evaluation of idiopathic pulmonary hypertension must exclude a secondary cause. A hypercoagulable state should be sought by measuring protein C and S levels, the presence of a lupus anticoagulant, the level of factor V Leiden, prothrombin gene mutations, and D-dimer. Chronic pulmonary emboli must be excluded (usually by ventilation-perfusion lung scan or contrast spiral CT); the ventilation-perfusion scan is the more sensitive test but not specific. If it is normal, then chronic thromboembolic pulmonary hypertension is very unlikely. The chest radiograph helps exclude a primary pulmonary etiology—evidence for patchy pulmonary edema may raise the suspicion of pulmonary veno-occlusive disease due to localized obstruction in pulmonary venous drainage. A sleep study may be warranted if sleep apnea is suspected. The ECG is generally consistent with RVH and RA enlargement. Echocardiography with Doppler helps exclude an intracardiac shunt and usually demonstrates an enlarged RV and RA—at times they may be huge and hypocontractile. Severe pulmonic or tricuspid valve regurgitation may be present. Interventricular septal flattening seen on the echocardiogram is consistent with pulmonary hypertension. Doppler interrogation of the tricuspid regurgitation jet provides an estimate of RV systolic pressure. Pulmonary function tests help exclude other disorders, though primary pulmonary hypertension may present with only a reduced carbon monoxide diffusing capacity of the lung (DL_{CO}) or severe desaturation (particularly if a

PFO has been stretched open and a right-to-left shunt is present). A declining DL_{CO} may precede the development of pulmonary hypertension in a patient with systemic sclerosis. Chest CT demonstrates enlarged pulmonary arteries and excludes other causes (such as emphysema or interstitial lung disease). Pulmonary angiography (or magnetic resonance angiography or CT angiography) reveals loss of the smaller acinar pulmonary vessels and tapering of the larger ones. Catheterization allows measurement of pulmonary pressures and testing for vasoreactivity using a variety of agents, but **nitric oxide** is the preferred testing agent due to its ease of use and short half-life. A positive response is defined as one that decreases the pulmonary mean pressure by greater than 10 mm Hg, with the final mean PA pressure less than 40 mm Hg. Abdominal ultrasound is recommended to exclude portal hypertension. A lung biopsy is no longer suggested as relevant for the diagnosis.

Treatment & Prognosis

The treatment of PAH continues to evolve and depends on the etiology. For group I patients with a normal PCWP, treatment is related to the response to nitric oxide challenge with those responsive being initially treated with calcium channel blockers. The vast majority of patients, unfortunately, do not respond to the acute vasoreactivity testing. Specific PAH therapy is therefore recommended in this situation. This begins with monotherapy but expands to the use of sequential medication therapy when pulmonary pressures are not improved. In critically ill hypotensive patients inotropic support may be required and eventually lung transplantation considered. Balloon atrial septostomy is considered a IIb recommendation (on the notion that increased right-to-left shunting will improve cardiac output), but it is very rarely utilized.

Medication monotherapy varies in effectiveness depending on the etiologic classification. Only those in class I who respond to nitric oxide should get calcium channel blockers. The current medication therapies include endothelin-receptor blockers (ambrisentan, bosentan, macitentan), phosphodiesterase type-5 inhibitors (sildenafil, tadalafil, and vardenafil), a guanylate cyclase stimulator (riociquat), prostanoids (epoprostenol, iloprost, teprostinil, and beraprost), and an IP-receptor agonist (selexipag). Various medication combinations have been approved and, when ineffective, sequential medication therapies may be used. Many medications interfere with HIV treatment, and this needs to be assessed if relevant. Due to inherent lung disease or left heart disease, there are no therapies that are specific to PAH. Bosentan, an endothelin receptor blocker, has received a class I indication for patients with Eisenmenger syndrome. Anticoagulation is often recommended and is required lifelong in chronic thromboembolic pulmonary hypertension. The number of patients with inoperable chronic thromboembolic pulmonary hypertension being treated with balloon pulmonary angioplasty has increased dramatically since favorable results have been reported. Riociguat remains the only approved medical therapy for chronic thromboembolic pulmonary hypertension patients in this latter group.

Counseling and patient education are also important. Aerobic exercise is recommended but no heavy physical exertion or isometric exercise. Routine immunizations are advised. Pregnancy should be strongly discouraged and preventive measures taken to ensure it does not occur. Maternal mortality in severe PAH may be up to 50%.

Warfarin anticoagulation is recommended in all patients with idiopathic PAH and no contraindication. Diuretics are useful for the management of right-sided heart failure; clinical experience suggests loop diuretics (torsemide or bumetanide, which are absorbed even if bowel edema is present) plus spironolactone are preferable. Oxygen should be used to maintain oxygen saturation greater than 90%. Acute vasodilator testing (generally with nitric oxide) should be performed in all patients with idiopathic PAH who may be potential candidates for long-term therapy with calcium channel blockers. Patients with PAH caused by conditions other than idiopathic PAH respond poorly to oral calcium channel blockers, and there is little value of acute vasodilator testing in these patients.

When to Refer

All patients with suspected pulmonary hypertension should be referred to either a cardiologist or pulmonologist who specializes in pulmonary hypertension.

Frost A et al. Diagnosis of pulmonary hypertension. Eur Respir J. 2019;53:1801904. [PMID: 30545972]
Galiè N et al. An overview of the 6th World Symposium on Pulmonary Hypertension. Eur Respir J. 2019;53:1802148. [PMID: 30552088]
Kataoka M et al. Balloon pulmonary angioplasty (percutaneous transluminal pulmonary angioplasty) for chronic thromboembolic pulmonary hypertension: a Japanese perspective. JACC Cardiovasc Interv. 2019;12:1382. [PMID: 31103538]
Simonneau G et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53:1801913. [PMID: 30545968]

NEOPLASTIC DISEASES OF THE HEART

PRIMARY CARDIAC TUMORS

Primary cardiac tumors are rare and constitute only a small fraction of all tumors that involve the heart or pericardium. The most common primary tumor is **atrial myxoma**; it comprises about 50% of all tumors in adult case series. It is generally attached to the atrial septum and is more likely to grow on the LA side of the septum rather than the RA. Patients with myxoma can rarely present with the characteristics of a systemic illness, with obstruction of blood flow at the mitral valve level, or with signs of peripheral embolization. The syndrome includes fever, malaise, weight loss, leukocytosis, elevated ESR, and emboli (peripheral or pulmonary, depending on the location of the tumor). This is sometimes confused with infective endocarditis, lymphoma, other cancers, or autoimmune diseases. In most cases, the tumor may grow to considerable size and produce symptoms by simply obstructing mitral inflow. Episodic pulmonary edema (classically occurring

when an upright posture is assumed) and signs of low output may result. Physical examination may reveal a diastolic sound related to motion of the tumor ("tumor plop") or a diastolic murmur similar to that of mitral stenosis. Right-sided myxomas may cause symptoms of right-sided failure. Familial myxomas occur as part of the Carney complex, which consists of myxomas, pigmented skin lesions, and endocrine neoplasia.

The diagnosis of atrial myxoma is established by echocardiography or by pathologic study of embolic material. Cardiac MRI is useful as an adjunct. Contrast angiography is frequently unnecessary, although it may demonstrate a "tumor blush" when the mass is vascular. Surgical excision is usually curative, though recurrences do occur and serial echocardiographic follow-up is recommended.

The second most common primary cardiac tumors are **valvular papillary fibroelastomas** and **atrial septal lipomas.** These tend to be benign and usually require no therapy. Papillary fibroelastomas are usually on the pulmonary or aortic valves, may embolize or cause valvular dysfunction, and should be removed if large and mobile. Other primary cardiac tumors include rhabdomyomas (that often appear multiple in both the RV and LV), fibrous histiocytomas, hemangiomas, and a variety of unusual sarcomas. Some sarcomas may be of considerable size before discovery. Primary pericardial tumors, such as mesotheliomas related to asbestos exposure, may also occur. The diagnosis may be supported by an abnormal cardiac contour on radiograph. Echocardiography is usually helpful but may miss tumors infiltrating the ventricular wall. Cardiac MRI is the diagnostic procedure of choice along with gated CT imaging for all cardiac tumors.

SECONDARY CARDIAC TUMORS

Metastases from malignant tumors can also affect the heart. Most often this occurs in malignant melanoma, but other tumors that are known to metastasize to the heart include bronchogenic carcinoma; carcinoma of the breast; lymphoma; renal cell carcinoma; sarcomas; and, in patients with AIDS, Kaposi sarcoma. These are often clinically silent but may lead to pericardial tamponade, arrhythmias and conduction disturbances, heart failure, and peripheral emboli. The ECG may reveal regional Q waves. The diagnosis is often made by echocardiography, but cardiac MRI and CT scanning can often better delineate the extent of involvement. Metastatic tumors, especially lung or breast, may invade the pericardium and result in very large pericardial effusions as they result in slow accumulation of fluid. The prognosis is poor for all secondary cardiac tumors and treatment is generally palliative. On occasion, surgical resection for debulking or removal and chemotherapy may be effective in relieving symptoms.

Treatment

Many primary tumors may be resectable. Atrial myxomas should be removed surgically due to the high incidence of embolization from these friable tumors. Recurrences require lifelong monitoring with echocardiography. Papillary fibroelastomas are usually benign but they should be removed if they appear mobile and are larger than 10 mm in size or if there is evidence of embolization at the time of discovery. Large pericardial effusions from metastatic tumors may be drained for comfort, but the fluid invariably recurs. Rhabdomyomas may be surgically cured if the tumor is accessible and can be removed while still leaving enough functioning myocardium intact.

When to Refer

All patients with suspected cardiac tumors should be referred to a cardiologist or cardiac surgeon for evaluation and possible therapy.

Rahouma M et al. Cardiac tumors prevalence and mortality: a systematic review and meta-analysis. Int J Surg. 2020;76:178. [PMID: 32169566]

TRAUMATIC HEART DISEASE

Trauma is the leading cause of death in patients aged 1–44 years; cardiac and vascular trauma is second only to neurologic injury as the reason for these deaths. Penetrating wounds to the heart are often lethal unless immediately surgically repaired. In a 20-year review of penetrating trauma at a single institution, it was found that gunshot wounds were fatal 13 times more often than stab wounds and that factors such as hypotension, Glasgow Coma Score less than 8, Revised Trauma Score less than 7.84, associated injuries, and the more severe the injuries (Injury Severity Score greater than 25) all added to the mortality and morbidity risk.

Blunt trauma is a more frequent cause of cardiac injuries. This type of injury is common in motor vehicle accidents and may occur with any form of chest trauma, including CPR efforts. The most common injuries are myocardial contusions or hematomas. The RV is particularly prone to contusion as it sits directly under the sternum. Other forms of nonischemic cardiac injury include metabolic injury due to burns, electrical current, or sepsis. These may be asymptomatic (particularly in the setting of more severe injuries) or may present with chest pain of a nonspecific nature or, not uncommonly, with a pericardial component. Elevations of cardiac enzymes are frequent, and can be quite high, but the levels do not correlate with prognosis. There are some data that the presence of certain other cardiac biomarkers, such as NT-proBNP, correlate better with significant myocardial injury. Echocardiography may reveal an akinetic myocardial segment or pericardial effusion. Cardiac MRI may also suggest acute injury. Coronary CT angiography or angiography can reveal a coronary dissection or acute occlusion if that is a concern. Pericardiocentesis is warranted if tamponade is evident. As noted above, tako-tsubo transient segmental myocardial dysfunction can occur due to the accompanying stress.

Severe trauma may also cause myocardial or valvular rupture. Cardiac rupture can involve any chamber, but survival is most likely if injury is to one of the atria or the RV. Hemopericardium or pericardial tamponade is the usual clinical presentation, and surgery is almost always necessary. Mitral and aortic valve rupture may occur during severe blunt trauma—the former presumably if the

impact occurs during systole and the latter if during diastole. Patients reach the hospital in shock or severe heart failure. Immediate surgical repair is essential. The same types of injuries may result in transection of the aorta, either at the level of the arch or distal to the takeoff of the left subclavian artery at the ligamentum arteriosum. Transthoracic echocardiography and TEE are the most helpful and immediately available diagnostic techniques. CT and MRI may also be required to better define the injury before surgical intervention.

Blunt trauma may also result in damage to the coronary arteries. Acute or subacute coronary thrombosis is the most common presentation. The clinical syndrome is one of acute MI with attendant ECG, enzymatic, and contractile abnormalities. Emergent revascularization is sometimes feasible, either by the percutaneous route or by coronary artery bypass surgery. LV aneurysms are common outcomes of traumatic coronary occlusions, likely due to sudden occlusion with no collateral vascular support. Coronary artery dissection or rupture may also occur in the setting of blunt cardiac trauma.

As expected, patients with severe preexisting conditions fare the least well after cardiac trauma. Data from ReCONECT, a trauma consortium, reveal that mortality is linked to volume of cases seen at various centers, preexisting coronary disease or heart failure, intubation, age, and a severity scoring index.

Qamar SR et al. State of the art imaging review of blunt and penetrating cardiac trauma. Can Assoc Radiol J. 2020;71:301. [PMID: 32066272]

Schellenberg M et al. Critical decisions in the management of thoracic trauma. Emerg Med Clin North Am. 2018;36:135. [PMID: 29132573]

HEART DISEASE & PREGNANCY

General principles to discuss with the patient include preconceptual counseling, pregnancy risk assessment, genetic risks, environmental risks, and pregnancy management. For some patients, it may also include a discussion regarding contraception, termination of a pregnancy, and a conversation about not only the delivery but what will happen post-pregnancy (including issues such as an eventual need for heart surgery or transplantation). In a review of 1315 pregnancies in patients with heart disease, 3.6% had serious cardiovascular complications and half were found to be preventable. Two-thirds of the complications occurred in the antepartum period. Adverse fetal and neonatal events, as expected, were much more common in those pregnancies with cardiovascular events.

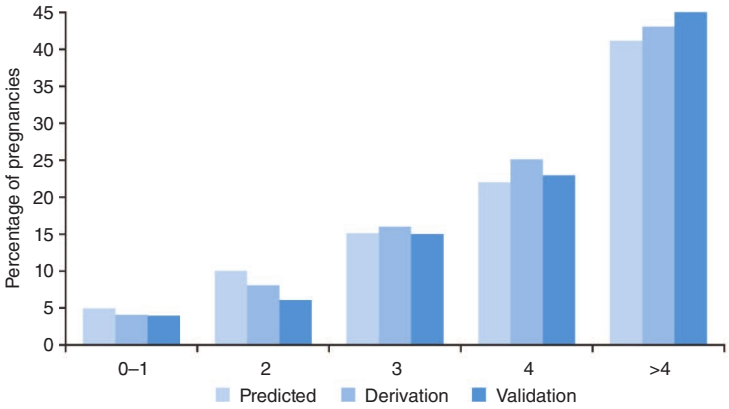
The **Cardiac Disease in Pregnancy Investigation (CARPREG I)** scoring system for risk from cardiac events for women with heart disease noted four major risk factors: (1) NYHA FC III or IV heart failure, (2) prior cardiac events, (3) mitral or aortic obstruction, and (4) LVEF less than 40%. One point is assigned to each. Patients with no points had a 5% risk, those with 1 point had a complication rate of 27%, while for those with 2 or more points, the risk was 74%. Other reviews have suggested that the major risk for adverse outcomes or death to either the mother or fetus include pulmonary hypertension (with pulmonary pressure greater than three-quarters of systemic pressure), maternal cyanosis, systemic ventricular dysfunction, poor maternal functional class, severe left-sided valvular obstruction, aortic coarctation, significantly dilated aortic root, significant unrepaired heart defects, and warfarin therapy in patients with mechanical valves. In 2018, this group reported the results from a follow-up study (CARPREG II). Cardiac complications occurred in 16% of pregnancies and were primarily related to arrhythmias and heart failure. Although the overall rates of cardiac complications during pregnancy did not change over the years, the frequency of pulmonary edema decreased (8% from 1994 to 2001 vs. 4% from 2001 to 2014). Ten predictors of maternal cardiac complications were identified: five general predictors (prior cardiac events or arrhythmias, poor functional class or cyanosis, high-risk valve disease/LV outflow tract obstruction, systemic ventricular dysfunction, no prior cardiac interventions); four lesion-specific predictors (mechanical valves, high-risk aortopathies, pulmonary hypertension, CAD); and one delivery of care predictor (late pregnancy assessment). These 10 predictors were incorporated into a new risk index **(CARPREG II)** shown in Figure 10–11.

The World Health Organization offers guidelines for the management of pregnancy in patients with congenital heart disease. This 2011 guideline also outlines risks to the fetus. Table 10–18 summarizes the observations and recommendations. Medication usage during pregnancy is always a difficult decision since *most have not been studied*. ACE inhibitors and amiodarone are contraindicated. Beta-blockers (including labetalol, metoprolol, and sotalol), digoxin, and calcium channel blockers are generally well tolerated (especially nifedipine, amlodipine, or verapamil, although there is controversy with diltiazem). There are concerns about the use of atenolol and premature birth, and it should not be used. Labetalol has been found to be particularly useful for treating hypertension as has methyldopa (though this is rarely used). Diuretics can generally be given safely. Pregnancy is a hypercoagulable state; the use of warfarin is discussed above under valvular disease and congenital heart disease, but fundamentally the risk is dose related (not INR related) and warfarin can be used during the first trimester if the dose is 5 mg or less. For many patients, the most common potential complication is an atrial arrhythmia or systemic hypertension (systemic BP greater than 140/90 mm Hg). Patients should be hospitalized if BP exceeds 170/110 mm Hg.

Patients with adult congenital heart disease are at risk not only for cardiovascular events but also for obstetric events such as hypertension, preeclampsia, placenta previa or abruption, and early delivery.

Pfaller B et al. Preventing complications in pregnant women with cardiac disease. J Am Coll Cardiol. 2020;75:1443. [PMID: 32216913]

Schlichting LE et al. Maternal comorbidities and complications of delivery in pregnant women with congenital heart disease. J Am Coll Cardiol. 2019;73:2181. [PMID: 31047006]



PREDICTOR	POINTS
Prior cardiac events or arrhythmias	3
Baseline NYHA III-IV or cyanosis	3
Mechanical valve	3
Ventricular dysfunction	2
High-risk left-sided valve disease/ left ventricular outflow tract obstruction	2
Pulmonary hypertension	2
Coronary artery disease	2
High-risk aortopathy	2
No prior cardiac intervention	1
Late pregnancy assessment	1

▲ **Figure 10–11.** Risk index for material cardiac complications in pregnancy (CARPREG II). The risk index is divided into five categories based on the sum of the points for a given pregnancy: 0 to 1 point; 2 points; 3 points; 4 points; and > 4 points. The predicted risks for primary cardiac events stratified according to point score were 0 to 1 point (5%), 2 points (10%), 3 points (15%), 4 points (22%), and > 4 points (41%). NYHA, New York Heart Association. (Reproduced with permission from Silversides CK, Grewal J, Mason J, et al. Pregnancy outcomes in women with heart disease: the CARPREG II Study. J Am Coll Cardiol. 2018;71(21):2419–2430.)

CARDIOVASCULAR COMPLICATIONS OF PREGNANCY

Pregnancy-related hypertension (eclampsia and preeclampsia) is discussed in Chapter 19.

1. Cardiomyopathy of Pregnancy (Peripartum Cardiomyopathy)

In approximately 1 in 3000 to 4000 live births, dilated cardiomyopathy develops in the mother in the final month of pregnancy or within 6 months after delivery. Risk factors include preeclampsia, twin pregnancies, and African ethnicity. The cause is slowly being elucidated. The vasculohormonal hypothesis requires two events. One is genetic, a reduction in a STAT3 transcription factor that results in cleavage of prolactin from the pituitary by cathepsin D. This results in a 16-kd fragment that increases microRNA 146a that results in myocardial apoptosis. The second is from the placenta, soluble tyrosine kinase that blocks VEGF (vascular endothelial growth factor). It appears both components may be necessary to effectively result in peripartum cardiomyopathy. The course of the disease is variable; most cases improve or resolve completely over several months, but others progress to refractory heart failure. About 60% of patients make a complete recovery. Serum BNP levels are routinely elevated in pregnancy, but serial values may be useful in predicting who may be at increased risk for a worse outcome. Beta-blockers have been administered judiciously to these patients, with at least anecdotal success. Diuretics, hydralazine, and nitrates help treat the heart failure with minimal risk to the fetus. Sotalol is acceptable for ventricular or atrial arrhythmias if other beta-blockers are ineffective. Some experts advocate anticoagulation because of an increased risk of thrombotic events, and both warfarin and heparin have their proponents. In severe cases, transient use of extracorporeal membrane oxygenation (ECMO) has been lifesaving. Recurrence in subsequent pregnancies is common, particularly if cardiac function has not completely recovered, and subsequent pregnancies are to be discouraged if the EF remains less than 55%. The risk of recurrent heart failure in a subsequent pregnancy has been estimated to be 21%. Delivery of the baby is important, though the peak incidence of the problem is in the first week after delivery and a few cases appear up to 5 weeks after delivery. Since the anti-angiogenic cleaved prolactin fragment is considered causal for peripartum cardiomyopathy, bromocriptine (a prolactin release inhibitor) has been reported to be beneficial. A multicenter trial in Europe found LVEF improved to a greater extent in patients with peripartum cardiomyopathy who were given bromocriptine than those who were not given bromocriptine. In addition, bromocriptine treatment was associated with high rate of full LV recovery and low morbidity and mortality in peripartum cardiomyopathy patients compared with other peripartum cardiomyopathy cohorts not treated with bromocriptine.

For a complete review of the current issues surrounding peripartum cardiomyopathy, the reader is referred to the state-of-art article noted below.

Davis MB et al. Peripartum cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75:207. [PMID: 31948651]
Honigberg MC et al. Peripartum cardiomyopathy. BMJ. 2019;364:k5287. [PMID: 30700415]

2. Coronary Artery & Aortic Vascular Abnormalities During Pregnancy

An acute coronary syndrome occurs in 2.8–8.1 per 1,000,000 pregnancies. Many are women over 35 years. It is known that pregnancy predisposes to dissection of the aorta

Table 10–18. Management strategies for women with valve disease, complex congenital heart disease, pulmonary hypertension, aortopathy, and dilated cardiomyopathy.

High-Risk Heart Disease in Pregnancy
- Preconception counseling and pregnancy risk stratification for all women with high-risk heart disease of childbearing age
- In women considering pregnancy: Switch to safer cardiac medications and emphasize importance of close monitoring
- In women avoiding pregnancy: Discuss safe and effective contraception choices or termination in early pregnancy

	Management Strategy		
Disease	**Pregnancy Not Advised**	**Pregnancy Management**	**Delivery**
Valve disease	• Severe mitral and aortic valve disease • Mechanical prosthetic valves if effective anticoagulation not possible	• Close follow-up • Medication therapy for heart failure or arrhythmias • Balloon valvuloplasty or surgical valve replacement in refractory cases	• Vaginal delivery preferred • C-section in case of fetal or maternal instability • Early delivery for clinical and hemodynamic deterioration • Consider hemodynamic monitoring during labor and delivery
Complex congenital heart disease	• Significant ventricular dysfunction • Severe AV valve dysfunction • Falling Fontan circulation • Oxygen saturation < 85%	• Close follow-up	• Vaginal delivery preferred • C-section in case of fetal or maternal instability • Consider hemodynamic monitoring during labor and delivery
Pulmonary hypertension	• Established pulmonary arterial hypertension	• Close follow-up • Early institution of pulmonary vasodilators	• Vaginal delivery preferred • C-section in case of fetal or maternal instability • Timing of delivery depends on clinical and RV function • Early delivery advisable • Diuresis after delivery to prevent RV volume overload • Extended hospital stay after delivery
Aortopathy	***For some women—*** • Marfan syndrome • Bicuspid aortic valve • Turner syndrome • Rapid growth of aortic diameter or family history of premature aortic dissection	• Treat hypertension • Beta-blockers to reduce heart rate • Frequent echocardiographic assessment • Surgery during pregnancy or after C-section if large increase in aortic diameter	• C-section in cases of significant aortic dilation – Marfan syndrome > 40 mm – Bicuspid aortic valve > 45 mm – Turner syndrome: aortic size index > 20 mm/m^2
Dilated cardiomyopathy	• LVEF < 40% • History of peripartum cardiomyopathy	• Close follow-up • Beta-blockers • Diuretic agents for volume overload • Vasodilators for hemodynamic and symptomatic improvement	• Vaginal delivery preferred • C-section in case of fetal or maternal instability • Consider hemodynamic monitoring during labor and delivery • Early delivery for clinical and hemodynamic deterioration

AV, atrioventricular; C-section, cesarean section; RV, right ventricular.
Reproduced with permission from Elkayam U et al. High-risk cardiac disease in pregnancy: Part I. J Am Coll Cardiol. 2016;68(4):396–410.

and other arteries, perhaps because of the accompanying connective tissue changes. The risks are particularly high in patients with Marfan, Ehlers-Danlos, or Loeys-Dietz syndromes. The risk is highest in the third trimester, and coronary dissection, thrombosis, and atherosclerosis have about equal prevalence. The most frequent cause in one study was coronary dissection, and it has a peak incidence in the early postpartum period. Paradoxical emboli through a PFO to the coronary arteries have been implicated in a few instances. Clinical management is essentially similar to that of other patients with acute infarction, unless there is a connective tissue disorder. If nonatherosclerotic dissection is present, coronary intervention may be risky, as further dissection can be aggravated. In most instances, conservative management is warranted. At times, extensive aortic dissection requires surgical intervention. Marfan patients are particularly susceptible to further aortic expansion during pregnancy when the aortic diameter is more than 4.5 cm

(greater or equal to 27 mm/m^2), and pregnancy should be discouraged in these situations. Some data, however, suggest that there is an increased risk of dissection during pregnancy even when the elective repair is reasonable (ie, when the aortic root is greater than 4.0 cm in women with Marfan syndrome contemplating pregnancy). Acute infarction during pregnancy is associated with an 8% maternal mortality and 56% incidence of premature delivery. If PCI is required, it is now recommended that a drug-eluting stent be considered rather than a bare metal stent. Medications that appear to be safe during pregnancy include aspirin, beta-blockers, clopidogrel, heparin or enoxaparin, and nitrates. Medications that are not safe include aldosterone inhibitors, ACE inhibitors or ARBs, DOACs, and statins. If need be, fibrinolytics, GP IIb/IIIa inhibitors, bivalirudin, and calcium channel blockers can be used.

Tweet MS et al. Pregnancy-associated myocardial infarction: prevalence, causes, and interventional management. Circ Cardiovasc Interv. 2020 Aug 1. [Epub ahead of print] [PMID: 32862672]

3. Management of Labor

Although vaginal delivery is usually well tolerated, unstable patients (including patients with severe hypertension and worsening heart failure) should have planned cesarean section. Spinal anesthesia results in a large drop in the systemic vascular resistance and can worsen right-to-left shunting. An increased risk of aortic rupture has been noted during delivery in patients with coarctation of the aorta and severe aortic root dilation with Marfan syndrome, and vaginal delivery should be avoided in these patients. For most patients, even those with complex congenital heart disease, vaginal delivery is the preferred method, however. Immediately following delivery, there are numerous fluid shifts that occur with the initial blood loss, reducing preload and accompanied by the loss of afterload reduction that had been provided by the placenta. Quickly, however, venous return increases as the uterus is no longer compressing the inferior vena cava and there is an infusion of fluid into the vascular system as the uterus quickly shrinks back toward its normal size. The sudden increase in preload and loss of afterload following delivery can result in heart failure during the first 48–72 hours after the delivery and that remains the high-risk time for susceptible patients.

CARDIOVASCULAR SCREENING OF ATHLETES

The sudden death of a competitive athlete inevitably becomes an occasion for local, if not national, publicity. On each occasion, the public and the medical community ask whether such events could be prevented by more careful or complete screening. Although each event is tragic, it must be appreciated that there are approximately 5 million competitive athletes at the high school level or above in any given year in the United States. The number of cardiac deaths occurring during athletic participation is unknown but estimates at the high school level range from one in 100,000 to one in 300,000 participants. Death rates among more mature athletes increase as the prevalence of CAD rises. These numbers highlight the problem of how best to screen individual participants. Even an inexpensive test such as an ECG would generate an enormous cost if required of all athletes, and it is likely that only a few at-risk individuals would be detected. Echocardiography, either as a routine test or as a follow-up examination for abnormal ECGs, would be prohibitively expensive except for the elite professional athlete. Thus, *the most feasible approach is that of a careful medical history and cardiac examination performed by personnel aware of the conditions responsible for most sudden deaths in competitive athletes.*

It is important to point out that sudden death is much more common in the older than the younger athlete. Older athletes will generally seek advice regarding their fitness for participation. These individuals should recognize that strenuous exercise is associated with an increase in risk of sudden cardiac death and that appropriate training substantially reduces this risk. Preparticipation screening for risk of sudden death in the older athlete is a complex issue and at present is largely focused on identifying inducible ischemia due to significant coronary disease.

In a series of 158 athletic deaths in the United States between 1985 and 1995, hypertrophic cardiomyopathy (36%) and coronary anomalies (19%) were by far the most frequent underlying conditions. LVH was present in another 10%, ruptured aorta (presumably due to Marfan syndrome or cystic medial necrosis) in 6%, myocarditis or dilated cardiomyopathy in 6%, aortic stenosis in 4%, and arrhythmogenic RV dysplasia in 3%. In addition, commotio cordis, or sudden death due to direct myocardial injury, may occur. More common in children, ventricular tachycardia or ventricular fibrillation may occur even after a minor direct blow to the heart; it is thought to be due to the precipitation of a PVC just prior to the peak of the T wave on ECG.

A careful family and medical history and cardiovascular examination will identify most individuals at risk. An update in 2014 recommends that **all middle school and higher athletes undergo a medical screen questionnaire and examination.** The 12 elements in the examination are outlined in Table 10–19.

A family history of premature sudden death or CVD, or of any of these predisposing conditions should mandate further workup, including an ECG and echocardiogram. Symptoms of unexplained fatigue or dyspnea, exertional chest pain, syncope, or near syncope also warrant further evaluation. A Marfan-like appearance, significant elevation of BP, abnormalities of heart rate or rhythm, and pathologic heart murmurs or heart sounds should also be investigated before clearance for athletic participation is given. Such an evaluation is recommended before participation at the high school and college levels and every 2 years during athletic competition.

Stress-induced syncope or chest pressure may be the first clue to an anomalous origin of a coronary artery. Anatomically, this lesion occurs most often when the left anterior descending artery or left main coronary arises from

Table 10–19. 12-element AHA recommendations for preparticipation cardiovascular screening of competitive athletes.

Medical History
Personal History
1. Exertional chest pain/discomfort
2. Unexplained syncope/near-syncope
3. Excessive exertional and unexplained dyspnea/fatigue
4. Prior recognition of a heart murmur
5. Elevated systemic blood pressure
Family History
6. Premature death (sudden and unexpected, or otherwise) before age of 50 years due to heart disease in one or more relatives
7. Disability from heart disease in a close relative before age of 50 years
8. Specific knowledge of certain cardiac conditions in family members: hypertrophic cardiomyopathy, dilated cardiomyopathy, long QT syndrome or other ion channelopathies, Marfan syndrome, or other important arrhythmias
Physical Examination
9. Heart murmur
10. Diminished femoral pulse (to exclude coarctation)
11. Phenotype of Marfan syndrome
12. Brachial artery blood pressure (sitting position)

Reproduced with permission from Lawless CE, Asplund C, Asif IM, et al. Protecting the heart of the American athlete: proceedings of the American College of Cardiology Sports and Exercise Cardiology Think Tank October 18, 2012, Washington, DC. J Am Coll Cardiol. 2014;64(20):2146–2171.

the right coronary cusp and traverses between the aorta and pulmonary trunks. The "slit-like" orifice that results from the angulation at the vessel origin is thought to cause ischemia when the aorta and pulmonary arteries enlarge during vigorous exercise and tension is placed on the coronary.

The toughest distinction may be in sorting out the healthy athlete with LVH from the athlete with hypertrophic cardiomyopathy. In general, the healthy athlete's heart is *less* likely to have an unusual pattern of LVH (such as asymmetric septal hypertrophy), or to have LA enlargement, an abnormal ECG, an LV cavity less than 45 mm in diameter at end-diastole, an abnormal diastolic filling pattern, or a family history of hypertrophic cardiomyopathy. The athlete is more likely to be male than the individual with hypertrophic cardiomyopathy, where women are equally at risk. Cardiac MRI is emerging as a useful means to separate the athlete's heart from hypertrophic obstructive cardiomyopathy. Increased risk is also evident in patients with the WPW syndrome, a prolonged QTc interval, or those who demonstrate the abnormal ST changes in leads V1 and V2 consistent with the Brugada syndrome.

Selective use of routine ECG and stress testing is recommended in men above age 40 years and women above age 50 years who continue to participate in vigorous exercise and at earlier ages when there is a positive family history for premature CAD, hypertrophic cardiomyopathy, or multiple risk factors. Because at least some of the risk features (long QT, LVH, Brugada syndrome, WPW syndrome) may be evident on routine ECG screening, several cost-effectiveness studies have been done. Most suggest that preparticipation ECGs are of potential value, though what to do when the QTc is mildly increased is unclear. Many experts feel the high incidence of false-positive ECG studies makes it very ineffective as a screening tool. With the low prevalence of cardiac anomalies in the general public, it has been estimated that 200,000 individual athletes would need to be screened to identify the single individual who would die suddenly. A report from Canada reviewing 74 sudden cardiac arrests during sports activity noted that the vast majority occurred during noncompetitive sports. The incidence during competitive sports was 0.76 per 100,000 athlete-years, and there was not a clear association with structural heart disease in most. Genetic testing of all athletes who demonstrate T-wave inversions on their ECG also has been shown to be ineffective; the genetic testing contributed an additional diagnosis in only 2.5% of subjects over that obtained by routine clinical means.

The issue of routine screening, therefore, remains controversial. A report from the United Kingdom in 2018, screening adolescent soccer players from 1996 to 2016 (that included ECG and echocardiography), identified diseases associated with sudden death in only 0.38% of the 11,168 athletes screened for a total of 118,351 person-years. The incidence of sudden death was about 7 per 100,000 athletes and most were related to cardiomyopathies that had not been detected on the screening procedures.

In 2017, a position paper from a number of European societies presented arguments regarding the use of a number of preparticipation screening options. The manuscript also provided input from a number of international sports organizations. They concluded that there were data to support obtaining the clinical history, performing a physical examination, and performing a 12-lead ECG on all participants. They did not recommend echocardiography as a screening tool.

In 2017, a consensus statement from the American Medical Society for Sports Medicine was published summarizing the current recommendations for the appropriate screening options in the various clinical scenarios. Once a high-risk individual has been identified, guidelines from the Bethesda conference and the ESC can be used to help determine whether the athlete may continue to participate in sporting events. Table 10–20 summarizes these recommendations.

Screening for return to play after myocardial/pericardial involvement with COVID-19 is currently an important issue (see also Infectious Myocarditis above). An expert consensus statement from the ACC suggests the following:

1. In the athlete who has had COVID-19, the ECG and high-sensitivity troponin should be normal. If any clinical concerns remain, then a transthoracic echocardiogram should be obtained.

Table 10–20. Recommendations for competitive sports participation among athletes with potential causes of SCD.

Condition	36th Bethesda Conference	European Society of Cardiology
Structural Cardiac Abnormalities		
HCM	Exclude athletes with a probable or definitive clinical diagnosis from all competitive sports. Genotype-positive/phenotype-negative athletes may still compete.	Exclude athletes with a probable or definitive clinical diagnosis from all competitive sports. Exclude genotype-positive/phenotype-negative individuals from competitive sports.
ARVC	Exclude athletes with a probable or definitive diagnosis from competitive sports.	Exclude athletes with a probable or definitive diagnosis from competitive sports.
CCAA	Exclude from competitive sports.	Not applicable.
	Participation in all sports 3 months after successful surgery would be permitted for an athlete with ischemia, ventricular arrhythmia or tachyarrhythmia, or LV dysfunction during maximal exercise testing.	
Electrical Cardiac Abnormalities		
WPW	Athletes without structural heart disease, without a history of palpitations, or without tachycardia can participate in all competitive sports. In athletes with symptoms, electrophysiological study and ablation are recommended. Return to competitive sports is allowed after corrective ablation, provided that the ECG has normalized.	Athletes without structural heart disease, without a history of palpitations, or without tachycardia can participate in all competitive sports. In athletes with symptoms, electrophysiological study and ablation are recommended. Return to competitive sports is allowed after corrective ablation, provided that the ECG has normalized.
LQTS	Exclude any athlete with a previous cardiac arrest or syncopal episode from competitive sports. Asymptomatic patients restricted to competitive low-intensity sports. Genotype-positive/phenotype-negative athletes may still compete.	Exclude any athlete with a clinical or genotype diagnosis from competitive sports.
BrS	Exclude from all competitive sports except those of low intensity.	Exclude from all competitive sports.
CPVT	Exclude all patients with a clinical diagnosis from competitive sports. Genotype-positive/phenotype-negative patients may still compete in low-intensity sports.	Exclude all patients with a clinical diagnosis from competitive sports. Genotype-positive/phenotype-negative patients are also excluded.
Acquired Cardiac Abnormalities		
Commotio cordis	Eligibility for returning to competitive sport in survivors is a matter of individual clinical judgment. Survivors must undergo a thorough cardiovascular workup including 12-lead ECG, ambulatory ECG monitoring, and echocardiography.	Not applicable.
Myocarditis	Exclude from all competitive sports. Convalescent period of 6 months. Athletes may return to competition when test results normalize.	Exclude from all competitive sports. Convalescent period of 6 months. Athletes may return to competition when test results normalize.

ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; CCAA, congenital coronary artery anomalies; CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; SCD, sudden cardiac death; WPW, Wolff-Parkinson-White syndrome.

Reproduced with permission from Chandra N et al. Sudden cardiac death in young athletes: practical challenges and diagnostic dilemmas. J Am Coll Cardiol. 2013;61(10):1027–1040.

2. Point-of-care echocardiography is not recommended, as the most common echocardiogram abnormalities may be missed by point-of-care echocardiography. These include RV dysfunction, diastolic LV abnormalities, and early signs of LV dysfunction (including abnormal global longitudinal strain). These are "red flags."
3. If any "red flags" from echocardiogram are present, then cardiac MRI should be obtained. MRI provides better assessment of RV function and abnormalities of myocardial edema (T2 imaging), intracellular and extracellular signaling (T1 imaging), and late gadolinium enhancement. The long-term significance of these findings is unknown.
4. Other imaging modalities can include coronary CT, chest CTA (looking for PE, given the hypercoagulable state COVID-19 creates), and rarely PET imaging.
5. Cardiopulmonary exercise testing is to be avoided during the acute phase but is valuable at 3–6 months after the illness if symptoms persist and as part of return to play guidelines.

Phelan D et al. Screening of potential cardiac involvement in competitive athletes recovering from COVID-19: an expert consensus statement. JACC Cardiovasc Imaging. 2020;13:2635. [PMID: 33303102]

11 Systemic Hypertension

Michael Sutters, MD, MRCP (UK)

Based on the National Health and Nutrition Survey period 2017–2018, about 45% of adults in the United States have a blood pressure greater than 130/80 mm Hg or are being treated for hypertension. About 80% of people with hypertension are aware of the diagnosis and 75% are receiving treatment, but hypertension is controlled in only 52% of those affected. Cardiovascular morbidity and mortality increase as both systolic and diastolic blood pressures rise, but in individuals over age 50 years, the systolic pressure and pulse pressure are better predictors of complications than diastolic pressure. The prevalence of hypertension increases with age. Adequate blood pressure control reduces the incidence of acute coronary syndrome by 20–25%, stroke by 30–35%, and heart failure by 50%.

HOW IS BLOOD PRESSURE MEASURED & HYPERTENSION DIAGNOSED?

Blood pressure should be measured with a well-calibrated sphygmomanometer. The bladder width within the cuff should encircle at least 80% of the arm circumference. Readings should be taken after the patient has been resting comfortably, back supported in the sitting or supine position, for at least 5 minutes and at least 30 minutes after smoking or coffee ingestion. Blood pressure readings made in the office with devices that permit multiple automated measurements after a pre-programmed rest period produce data that are independent of digit preference bias (tendency to favor numbers that end with zero or five) and avoid the "white coat" phenomenon (where blood pressure is elevated in the clinic but normal at home). Blood pressure measurements taken outside the office environment, either by intermittent self-monitoring (home blood pressure) or with an automated device programmed to take measurements at regular intervals (ambulatory blood pressure), are more powerful predictors of outcomes and are advocated in clinical guidelines.

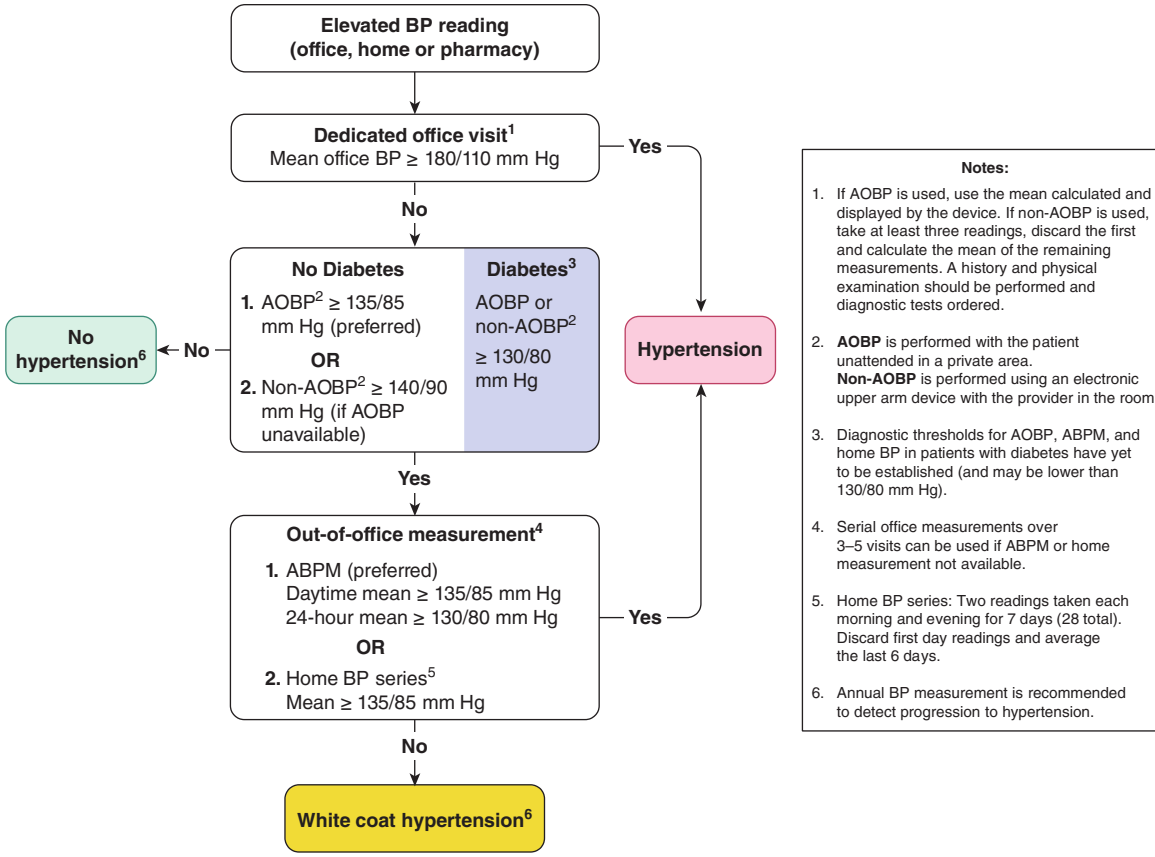
A single elevated blood pressure reading is not sufficient to establish the diagnosis of hypertension. The major exceptions to this rule are hypertension presenting with unequivocal evidence of life-threatening end-organ damage, as seen in hypertensive emergency, or hypertensive urgency where blood pressure is greater than 220/125 mm Hg but life-threatening end-organ damage is absent. In less severe cases, the diagnosis of hypertension depends on a series of measurements of blood pressure since readings can vary and tend to regress toward the mean with time. Patients whose initial blood pressure is in the hypertensive range exhibit the greatest fall toward the normal range between the first and second encounters. However, the concern for diagnostic precision needs to be balanced by an appreciation of the importance of establishing the diagnosis of hypertension as quickly as possible since a 3-month delay in treatment of hypertension in high-risk patients is associated with a twofold increase in cardiovascular morbidity and mortality. The 2017 guidelines from the American College of Cardiology and American Heart Association (ACC/AHA) (based on conventional office-based measurements) define **normal blood pressure** as less than 120/80 mm Hg, **elevated blood pressure** as 120–129/less than 80 mm Hg, **stage 1 hypertension** as 130–139/80–89 mm Hg, and **stage 2 hypertension** as greater than or equal to 140/90 mm Hg. As exemplified by Hypertension Canada's 2017 guidelines (Figure 11–1), automated and home blood pressure measurements have assumed greater prominence in the diagnostic algorithms published by many national hypertension workgroups. Equivalent blood pressures for these different modes of measurement are described in Table 11–1.

Blood pressure is normally lowest at night and the loss of this nocturnal dip is a dominant predictor of cardiovascular risk, particularly risk of thrombotic stroke. An accentuation of the normal morning increase in blood pressure is associated with increased likelihood of cerebral hemorrhage.

It is important to recognize that patients in whom hypertension is diagnosed do not automatically require drug treatment; this decision depends on the clinical setting and evaluation of cardiovascular risk.

White Coat, Masked, & Labile Hypertension

The term "white coat" hypertension applies to patients whose blood pressure is elevated in the office but normal at home. Cardiovascular risk in white coat hypertension is elevated but less so than in established hypertension. Masked hypertension describes the opposite situation,



▲ **Figure 11–1.** According to these recommendations, if AOBP measurements are not available, blood pressures recorded manually in the office may be substituted if taken as the mean of the last two readings of three consecutive readings. Note that the blood pressure threshold for diagnosing hypertension is higher if recorded manually in these guidelines. If home blood pressure monitoring is unavailable, office measurements recorded over three to five separate visits can be substituted. ABPM, ambulatory blood pressure measurement; AOBP, automated office blood pressure; BP, blood pressure. (Reproduced with permission from Leung AA, Daskalopoulou SS, Dasgupta K, et al. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. Can J Cardiol. 2017;33(5):557–576.)

Table 11–1. Corresponding blood pressure values across a range of blood pressure measurement methods.

Manual Measurement in Clinic[1]	Home Blood Pressure Measurement	Ambulatory Blood Pressure Measurement (Daytime)	Ambulatory Blood Pressure Measurement (Nighttime)	Ambulatory Blood Pressure Measurement (24-Hour)
120/80 mm Hg	120/80 mm Hg	120/80 mm Hg	100/65 mm Hg	115/75 mm Hg
130/80 mm Hg	130/80 mm Hg	130/80 mm Hg	110/65 mm Hg	125/75 mm Hg
140/90 mm Hg	135/85 mm Hg	135/85 mm Hg	120/70 mm Hg	130/80 mm Hg
160/100 mm Hg	145/90 mm Hg	145/90 mm Hg	140/85 mm Hg	145/90 mm Hg

[1]Clinic manual blood pressures are critically dependent on technique. The use of automated devices in an unattended setting typically result in systolic blood pressures 9–13 mm Hg lower than clinic manual pressures. Data abstracted from Greenland P et al. The New 2017 ACC/AHA Guidelines "up the pressure" on diagnosis and treatment of hypertension. JAMA. 2017;318:2083.

where blood pressure is normal in the office setting but elevated at home. Masked hypertension is associated with a cardiovascular risk at least as high as in established hypertension. Variability of systolic blood pressure, often described as labile hypertension, predicts cardiovascular events independently of mean systolic blood pressure.

Greenland P et al. The New 2017 ACC/AHA Guidelines "up the pressure" on diagnosis and treatment of hypertension. JAMA. 2017;318:2083. [PMID: 29159417]
Jin J. JAMA patient page. Checking blood pressure at home. JAMA. 2017;318:310. [PMID: 28719694]
Leung AA et al; Hypertension Canada. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. Can J Cardiol. 2017;33:557. [PMID: 28449828]
Melville S et al. Out-of-office blood pressure monitoring in 2018. JAMA. 2018;320:1805. [PMID: 30398589]

APPROACH TO HYPERTENSION

Etiology & Classification

A. Primary Essential Hypertension

"Essential hypertension" is the term applied to the 95% of hypertensive patients in which elevated blood pressure results from complex interactions between multiple genetic and environmental factors. The onset is usually between ages 25 and 50 years; it is uncommon before age 20 years. The best understood pathways underlying hypertension include overactivation of the sympathetic nervous and renin-angiotensin-aldosterone systems (RAAS), blunting of the pressure-natriuresis relationship, variation in cardiovascular and renal development, and elevated intracellular sodium and calcium levels.

Exacerbating factors include obesity, sleep apnea, increased salt intake, excessive alcohol use, cigarette smoking, polycythemia, NSAID therapy, and low potassium intake. Obesity is associated with an increase in intravascular volume; elevated cardiac output; activation of the renin-angiotensin system; and, probably, increased sympathetic outflow. Lifestyle-driven weight reduction lowers blood pressure modestly, but the dramatic weight reduction following bariatric surgery results in improved blood pressure in most patients, and actual remission of hypertension in 20–40% of cases. In patients with sleep apnea, treatment with continuous positive airway pressure (CPAP) has been associated with improvements in blood pressure. Increased salt intake probably elevates blood pressure in some individuals so dietary salt restriction is recommended in patients with hypertension. Excessive use of alcohol also raises blood pressure, perhaps by increasing plasma catecholamines. Hypertension can be difficult to control in patients who consume more than 40 g of ethanol (two drinks) daily or drink in "binges." Cigarette smoking raises blood pressure by increasing plasma norepinephrine. Although the long-term effect of smoking on blood pressure is less clear, the synergistic effects of smoking and high blood pressure on cardiovascular risk are well documented. The relationship of exercise to hypertension is variable. Aerobic exercise lowers blood pressure in previously sedentary individuals, but increasingly strenuous exercise in already active subjects has less effect. The relationship between stress and hypertension is not established. Polycythemia, whether primary, drug-induced, or due to diminished plasma volume, increases blood viscosity and may raise blood pressure. NSAIDs produce increases in blood pressure averaging 5 mm Hg and are best avoided in patients with borderline or elevated blood pressures. Low potassium intake is associated with higher blood pressure in some patients; an intake of 90 mmol/day is recommended.

The complex of abnormalities termed the **"metabolic syndrome"** (upper body obesity, insulin resistance, and hypertriglyceridemia) is associated with both the development of hypertension and an increased risk of adverse cardiovascular outcomes. Affected patients usually also have low HDL cholesterol levels and elevated catecholamines and inflammatory markers such as CRP.

B. Secondary Hypertension

Approximately 5% of patients have hypertension secondary to identifiable specific causes (Table 11–2). Secondary

Table 11–2. Causes of secondary hypertension.

Endocrine	
	Conn syndrome (hyperaldosteronism)
	Licorice
	Cushing syndrome (hypercortisolism)
	Thyroid disease
	Pheochromocytoma
	Acromegaly
	Mutations in steroid gene regulatory domains
	Hypercalcemia
Renal	
	Parenchymal kidney disease
	Polycystic kidney disease
	Systemic sclerosis (scleroderma)
	Page kidney (subcapsular compression of the kidney)
	Mutations in genes encoding ion transport proteins
Vascular	
	Renal artery stenosis
	Coarctation
Autonomic	
	Stress
	Neurogenic
Medications	
	NSAIDs
	Corticosteroids
	Calcineurin inhibitors
	Stimulants
	Decongestants
	Angiogenesis inhibitors
	Tyrosine kinase inhibitors
	Estrogen
	Erythropoietin
	Alcohol, cocaine
	Gemcitabine
	Atypical antipsychotics
	MAO inhibitors
Other	
	Obstructive sleep apnea
	Pregnancy

hypertension should be suspected in patients in whom hypertension develops at an early age or after the age of 50 years, and in those previously well controlled who become refractory to treatment. Hypertension resistant to maximum doses of three medications is another clue, although multiple medications are usually required to control hypertension in persons with diabetes.

1. Genetic causes—Hypertension can be caused by mutations in single genes, inherited on a Mendelian basis. Although rare, these conditions provide important insight into blood pressure regulation and possibly the genetic basis of essential hypertension. Glucocorticoid remediable aldosteronism is an autosomal dominant cause of early-onset hypertension with normal or high aldosterone and low renin levels. The syndrome of hypertension exacerbated in pregnancy is inherited as an autosomal dominant trait. In these patients, a mutation in the mineralocorticoid receptor makes it abnormally responsive to progesterone and, paradoxically, to spironolactone. Liddle syndrome is an autosomal dominant condition characterized by early-onset hypertension, hypokalemic alkalosis, low renin, and low aldosterone levels. Gordon syndrome, or pseudohypoaldosteronism type II, is most often transmitted in an autosomal dominant pattern and presents with early-onset hypertension associated with hyperkalemia, metabolic acidosis, and relative suppression of aldosterone.

2. Kidney disease—Renal parenchymal disease is the most common cause of secondary hypertension, which results from increased intravascular volume and increased activity of the RAAS. Increased sympathetic nerve activity may also contribute.

3. Renal vascular hypertension—Renal artery stenosis is present in 1–2% of hypertensive patients. The most common cause is atherosclerosis, but fibromuscular dysplasia should be suspected in women under 50 years of age. Excessive renin release occurs due to reduction in renal perfusion pressure, while attenuation of pressure natriuresis contributes to hypertension in patients with a single kidney or bilateral lesions.

Renal vascular hypertension should be suspected in the following circumstances: (1) the documented onset is before age 20 or after age 50 years, (2) the hypertension is resistant to three or more drugs, (3) there are epigastric or renal artery bruits, (4) there is atherosclerotic disease of the aorta or peripheral arteries (15–25% of patients with symptomatic lower limb atherosclerotic vascular disease have renal artery stenosis), (5) there is an abrupt increase (more than 25%) in the level of serum creatinine after administration of ACE inhibitors, or (6) episodes of pulmonary edema are associated with abrupt surges in blood pressure. (See Renal Artery Stenosis, Chapter 22.)

4. Primary hyperaldosteronism—Hyperaldosteronism should be considered in people with resistant hypertension, blood pressures consistently greater than 150/100 mm Hg, hypokalemia (although this is often absent), or adrenal incidentaloma, and in those with a family history of hyperaldosteronism. Mild hypernatremia and metabolic alkalosis may also occur. Hypersecretion of aldosterone is estimated to be present in 5–10% of hypertensive patients and, besides noncompliance, is the most common cause of resistant hypertension. The initial screening step is the simultaneous measurement of aldosterone and renin in blood in a morning sample collected after 30 minutes quietly seated. Hyperaldosteronism is suggested when the plasma aldosterone concentration is elevated (normal: 1–16 ng/dL) in association with suppression of plasma renin activity (normal: 1–2.5 ng/mL/hour). However, the plasma aldosterone/renin ratio (normal less than 30) is not highly specific as a screening test. This is because renin levels may approach zero, which leads to exponential increases in the plasma aldosterone/renin ratio even when aldosterone levels are normal. Hence, an elevated plasma aldosterone/renin ratio should probably not be taken as evidence of hyperaldosteronism unless the aldosterone level is actually elevated.

During the workup for hyperaldosteronism, an initial plasma aldosterone/renin ratio can be measured while the patient continues taking usual medications. If under these circumstances the ratio proves normal or equivocal, medications that alter renin and aldosterone levels, including ACE inhibitors, ARBs, diuretics, beta-blockers, and clonidine, should be discontinued for 2 weeks before repeating the plasma aldosterone/renin ratio; spironolactone and eplerenone should be held for 4 weeks. Slow-release verapamil and alpha-blockers can be used to control blood pressure during this drug washout period. Patients with a plasma aldosterone level greater than 16 ng/dL and an aldosterone/renin ratio of 30 or more might require further evaluation for primary hyperaldosteronism.

The lesion responsible for hyperaldosteronism is an adrenal adenoma or bilateral adrenal hyperplasia.

5. Cushing syndrome—Hypertension occurs in about 80% of patients with spontaneous Cushing syndrome. Excess glucocorticoid may act through salt and water retention (via mineralocorticoid effects), increased angiotensinogen levels, or permissive effects in the regulation of vascular tone. Diagnosis and treatment of Cushing syndrome are discussed in Chapter 26.

6. Pheochromocytoma—Pheochromocytomas are uncommon; they are probably found in less than 0.1% of all patients with hypertension and in approximately two individuals per million population. Chronic vasoconstriction of the arterial and venous beds leads to a reduction in plasma volume and predisposes to postural hypotension. Glucose intolerance develops in some patients. Hypertensive crisis in pheochromocytoma may be precipitated by a variety of drugs, including tricyclic antidepressants, antidopaminergic agents, metoclopramide, and naloxone. The diagnosis and treatment of pheochromocytoma are discussed in Chapter 26.

7. Coarctation of the aorta—This uncommon cause of hypertension is discussed in Chapter 10. Evidence of radial-femoral delay should be sought in all younger patients with hypertension.

8. Hypertension associated with pregnancy—Hypertension occurring de novo or worsening during pregnancy,

including preeclampsia and eclampsia, is one of the most common causes of maternal and fetal morbidity and mortality (see Chapter 19). Autoantibodies with the potential to activate the angiotensin II type 1 receptor have been causally implicated in preeclampsia, in resistant hypertension, and in progressive systemic sclerosis.

9. Estrogen use—A small increase in blood pressure occurs in most women taking oral contraceptives. A more significant increase of 8/6 mm Hg systolic/diastolic is noted in about 5% of women, mostly in obese individuals older than age 35 who have been treated for more than 5 years. This is caused by increased hepatic synthesis of angiotensinogen. The lower dose of postmenopausal estrogen does not generally cause hypertension but rather maintains endothelium-mediated vasodilation.

10. Other causes of secondary hypertension—Hypertension has been associated with hypercalcemia, acromegaly, hyperthyroidism, hypothyroidism, baroreceptor denervation (sometimes seen after treatment of head and neck cancer), compression of the rostral ventrolateral medulla, and increased intracranial pressure. Certain medications may cause or exacerbate hypertension—most importantly cyclosporine, tacrolimus, angiogenesis inhibitors, and erythrocyte-stimulating agents (such as erythropoietin). Decongestants, NSAIDs, cocaine, and alcohol should also be considered. Over-the-counter products should not be overlooked, eg, a dietary supplement marketed to enhance libido was found to contain yohimbine, an alpha-2–antagonist, which can produce severe rebound hypertension in patients taking clonidine.

When to Refer

Referral to a hypertension specialist should be considered in cases of severe, resistant, or early-/late-onset hypertension or when secondary hypertension is suggested by screening.

Byrd JB et al. Primary aldosteronism. Circulation. 2018;138:823. [PMID: 30359120]
Herrmann SM et al. Renovascular hypertension. Endocrinol Metab Clin North Am. 2019;48:765. [PMID: 31655775]

Complications of Untreated Hypertension

Many adverse outcomes in hypertension are associated with thrombosis rather than bleeding, possibly because increased vascular shear stress converts the normally anticoagulant endothelium to a prothrombotic state. The excess morbidity and mortality related to hypertension approximately doubles for each 6 mm Hg increase in diastolic blood pressure. However, target-organ damage varies markedly between individuals with similar levels of office hypertension; home and ambulatory pressures are superior to office readings in the prediction of end-organ damage (Table 11–1).

A. Hypertensive Cardiovascular Disease

Cardiac complications are the major causes of morbidity and mortality in primary (essential) hypertension. For any level of blood pressure, LVH is associated with incremental cardiovascular risk in association with heart failure (through systolic or diastolic dysfunction), ventricular arrhythmias, myocardial ischemia, and sudden death.

The occurrence of heart failure is reduced by 50% with antihypertensive therapy. Hypertensive LVH regresses with therapy and is most closely related to the degree of systolic blood pressure reduction. Diuretics have produced equal or greater reductions of LV mass when compared with other drug classes. Conventional beta-blockers are less effective in reducing LVH but play a specific role in patients with established CAD or impaired LV function.

B. Hypertensive Cerebrovascular Disease and Dementia

Hypertension is the major predisposing cause of hemorrhagic and ischemic stroke. Cerebrovascular complications are more closely correlated with systolic than diastolic blood pressure. The incidence of these complications is markedly reduced by antihypertensive therapy. Preceding hypertension is associated with a higher incidence of subsequent dementia of both vascular and Alzheimer types. Home and ambulatory blood pressure may be a better predictor of cognitive decline than office readings in older people. Effective blood pressure control reduces the risk of cognitive dysfunction developing later in life.

C. Hypertensive Kidney Disease

Chronic hypertension is associated with injury to vascular, glomerular, and tubulointerstitial compartments within the kidney, accounting for about 25% of ESKD. Nephrosclerosis is particularly prevalent in persons of sub-Saharan African ancestry, in whom susceptibility is linked to *APOL1* mutations and hypertension results from kidney disease rather than causing it.

D. Aortic Dissection

Hypertension is a contributing factor in many patients with dissection of the aorta. Its diagnosis and treatment are discussed in Chapter 12.

E. Atherosclerotic Complications

Most Americans with hypertension die of complications of atherosclerosis, but the impact of antihypertensive therapy on atherosclerotic complications is less clear than that seen in the prevention of heart failure, stroke, and kidney disease. Prevention of cardiovascular outcomes related to atherosclerosis probably requires control of multiple risk factors, of which hypertension is only one.

Supiano MA et al. New guidelines and SPRINT results: implications for geriatric hypertension. Circulation. 2019;140:976. [PMID: 31525101]

Clinical Findings

The clinical and laboratory findings arise from involvement of the target organs: heart, brain, kidneys, eyes, and peripheral arteries.

A. Symptoms

Mild to moderate primary (essential) hypertension is largely asymptomatic for many years. The most frequent symptom, headache, is also nonspecific. Accelerated hypertension is associated with somnolence, confusion, visual disturbances, and nausea and vomiting (hypertensive encephalopathy).

Hypertension in patients with pheochromocytomas that secrete predominantly norepinephrine is usually sustained but may be episodic. The typical attack lasts from minutes to hours and is associated with headache, anxiety, palpitation, profuse perspiration, pallor, tremor, and nausea and vomiting. Blood pressure is markedly elevated, and angina or acute pulmonary edema may occur. In primary aldosteronism, patients may have muscular weakness, polyuria, and nocturia due to hypokalemia; hypertensive emergency is rare. Chronic hypertension often leads to LVH and diastolic dysfunction, which can present with exertional and paroxysmal nocturnal dyspnea. Cerebral involvement causes stroke due to thrombosis or hemorrhage from microaneurysms of small penetrating intracranial arteries. Hypertensive encephalopathy is probably caused by acute capillary congestion and exudation with cerebral edema and may present as posterior reversible encephalopathy syndrome, comprising headache, visual disturbances, altered mental state, and seizures. These symptoms usually improve rapidly with control of hypertension.

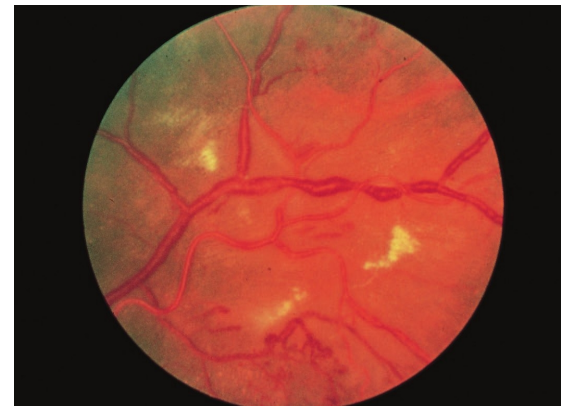
B. Signs

Like symptoms, physical findings depend on the cause of hypertension, its duration and severity, and the degree of effect on target organs.

1. Blood pressure—Blood pressure is taken in both arms and, if lower extremity pulses are diminished or delayed, in the legs to exclude coarctation of the aorta. If blood pressure differs between right and left arms, the higher reading should be recorded as the actual blood pressure and subclavian stenosis suspected in the other arm. An orthostatic drop of at least 20/10 mm Hg is often present in pheochromocytoma. Older patients may have falsely elevated readings by sphygmomanometry because of noncompressible vessels. This may be suspected in the presence of Osler sign—a palpable brachial or radial artery when the cuff is inflated above systolic pressure. Occasionally, it may be necessary to make direct measurements of intra-arterial pressure, especially in patients with apparent severe hypertension who do not tolerate therapy.

2. Retinas—Narrowing of arterial diameter to less than 50% of venous diameter, copper or silver wire appearance, exudates, hemorrhages, and hypertensive retinopathy are associated with a worse prognosis. The typical changes of severe hypertensive retinopathy are shown in Figure 11–2 (see Chapter 7).

3. Heart—An LV heave indicates severe hypertrophy. Aortic regurgitation may be auscultated in up to 5% of patients, and hemodynamically insignificant aortic regurgitation can be detected by Doppler echocardiography in 10–20%. A presystolic (S_4) gallop due to decreased compliance of the LV is quite common in patients in sinus rhythm.



▲ **Figure 11–2. Severe, chronic hypertensive retinopathy with hard exudates, increased vessel light reflexes, and sausage-shaped veins.** (Used, with permission, from Richard E. Wyszynski, MD, in Knoop KJ, Stack LB, Storrow AB, Thurman RJ. *The Atlas of Emergency Medicine*, 4th ed. McGraw-Hill, 2016.)

4. Pulses—Radial-femoral delay suggests coarctation of the aorta; loss of peripheral pulses occurs due to atherosclerosis, less commonly aortic dissection, and rarely Takayasu arteritis, all of which can involve the renal arteries.

C. Laboratory Findings

Recommended testing includes hemoglobin; serum electrolytes and serum creatinine; fasting blood sugar level (hypertension is a risk factor for the development of diabetes, and hyperglycemia can be a presenting feature of pheochromocytoma); plasma lipids (necessary to calculate cardiovascular risk and as a modifiable risk factor); serum uric acid (hyperuricemia is a relative contraindication to diuretic therapy); and UA.

D. ECG and Chest Radiographs

Electrocardiographic criteria are highly specific but not very sensitive for LVH. The "strain" pattern of ST–T wave changes is a sign of more advanced disease and is associated with a poor prognosis. A chest radiograph is not necessary in the workup of uncomplicated hypertension.

E. Echocardiography

The primary role of echocardiography should be to evaluate patients with clinical symptoms or signs of cardiac disease.

F. Diagnostic Studies

Additional diagnostic studies are indicated only if the clinical presentation or routine tests suggest secondary or

complicated hypertension. These may include 24-hour urine free cortisol, urine or plasma metanephrines, and plasma aldosterone and renin concentrations to screen for endocrine causes of hypertension. Renal ultrasound will detect structural changes (such as polycystic kidneys, asymmetry, and hydronephrosis); increased echogenicity and reduced cortical volume are reliable indicators of advanced CKD. Evaluation for renal artery stenosis should be undertaken in concert with subspecialist consultation.

G. Summary

Since most hypertension is essential or primary, few studies are necessary beyond those listed above. If conventional therapy is unsuccessful or if secondary hypertension is suspected, further studies and perhaps referral to a hypertension specialist are indicated.

Nonpharmacologic Therapy

Lifestyle modification is recommended for all patients with elevated blood pressure. A diet rich in fruits, vegetables, and low-fat dairy foods and low in saturated and total fats (DASH diet) has been shown to lower blood pressure. Increased dietary fiber lowers blood pressure. For every 7 g of dietary fiber ingested, cardiovascular risk could be lowered by 9%. The effect of diet on blood pressure may be mediated by shifts in the microbial species in the gut, the intestinal microbiota. Hand squeezing exercises three times a week can lower systolic blood pressure by 6 mm Hg. The protocol comprises four repeats of 2 minutes at 30% of maximum force (using a handheld dynamometer) with 1- to 3-minute rest intervals between squeezes. The acute increase in systolic blood pressure during vigorous exercise, known as the exercise pressor response, is around 50 mm Hg in normal individuals. In hypertensive persons, the exercise pressor response is elevated to about 75 mm Hg above resting systolic blood pressure. This exaggerated response is not reduced by antihypertensive medications, even in those with otherwise controlled hypertension, and is exacerbated by increased dietary sodium intake.

Additional lifestyle changes, listed in Table 11–3, can prevent or mitigate hypertension or its cardiovascular consequences.

Table 11–3. The impact of lifestyle modifications.

Modification	Intervention	Resulting Decrease in Blood Pressure
Weight loss	Target BMI 18.5–24.9	5–20 mm Hg/ 10-kg loss
DASH diet	Fruit, vegetables, low fat dairy	8–14 mm Hg
Sodium intake	< 100 mmol/day (< 6 g salt)	2–8 mm Hg
Alcohol intake	Male ≤ 2 drinks/day Female ≤ 1 drink/day	4 mm Hg
Exercise	Aerobic 30 minutes/day Dynamic 90-150 minutes/ week Isometric (hand grip 4 repetitions 3 times/week)	5–10 mm Hg
Mindfulness	Meditation and breathing control	5 mm Hg

DASH, Dietary Approaches to Stop Hypertension.

Fu J et al. Nonpharmacologic interventions for reducing blood pressure in adults with prehypertension to established hypertension. J Am Heart Assoc. 2020;9:e016804. [PMID: 32975166]

Smart NA et al. An evidence-based analysis of managing hypertension with isometric resistance exercise—are the guidelines current? Hypertens Res. 2020;43:249. [PMID: 31758166]

Who Should Be Treated With Medications?

Treatment should be offered to all persons in whom blood pressure reduction, irrespective of initial blood pressure levels, will reduce cardiovascular risk with an acceptably low rate of medication-associated adverse effects. The ACC/AHA, Hypertension Canada (HC), and the European Society of Hypertension and European Society of Cardiology (ESH/ESC) have developed independent guidelines for the evaluation and management of hypertension. There is broad agreement that drug treatment is necessary in those with office-based blood pressures exceeding 160/100 mm Hg, irrespective of cardiac risk. Similarly, the American, Canadian, and European guidelines agree that treatment thresholds should be lower in the presence of elevated cardiovascular risk. American guidelines stand apart in recommending initiation of antihypertensive pharmacotherapy in those with blood pressure of 140–159/90–99 mm Hg, even if cardiovascular risk is not elevated. By contrast, the Canadian guidelines suggest lifestyle modifications in this low-cardiovascular-risk group, while the European guidelines recommend initiation of pharmacotherapy only if elevated pressure in this low-risk population persists after lifestyle modification. There is no outcomes evidence that mortality or risk of cardiovascular events can be reduced by treating mild hypertension (140/90–160/100 mm Hg) in low-risk individuals. Table 11–4 compares these three sets of guidelines. Since evaluation of total cardiovascular risk (Table 11–5) is important in deciding who to treat with antihypertensive medications, risk calculators are essential clinical tools. The ACC has an online toolkit relevant to primary prevention (https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/), and an associated app called ASCVD Risk Estimator Plus (downloadable at https://www.acc.org/ASCVDApp). The interaction between risk and age deserves careful attention. At any given level of calculated risk, treatment is likely to have a greater impact in the young than the elderly. Consequently, there is a possibility that setting absolute risk thresholds for treatment might lead to undertreatment of the young and overtreatment of the elderly.

Table 11–4. Comparison of blood pressure treatment thresholds from the 2017 ACC/AHA guidelines, the 2018 Hypertension Canada guidelines, and the 2018 ESH/ESC guidelines.

Guidelines[1]	Cardiovascular Risk	Threshold for Pharmacotherapy (mm Hg)	Target (mm Hg)
ACC/AHA	Not increased	> 140/90	< 130/80 (reasonable)
Hypertension Canada	Not increased	> 160/100	< 140/90 (< 130/80 for diabetes)
ESH/ESC	Not increased	> 140/90[2]	All < 140/90, most < 130/80, not < 120
ACC/AHA	Increased	< 130/80	< 130/80 (recommended)
Hypertension Canada	Increased	> 140 systolic[3]	< 120 systolic
ESH/ESC	Increased	> 130/80	120–130/< 80
ACC/AHA > 65 yr	Risk due to advanced age	> 130/80	< 130 systolic
Hypertension Canada (for older adults)[4]	Increased	Not specified[4]	Not specified[4]
ESH/ESC > 65 yr	Not increased	> 140/90[5]	130–140/> 80[6]

[1]In all three sets of guidelines, blood pressure values are based on nonautomated office blood pressure readings.
[2]Consider drug treatment if lifestyle changes fail to control blood pressure.
[3]Consider drug treatment at systolic blood pressure > 130 mm Hg if very high risk, eg, established cardiovascular disease, especially coronary disease. **Note:** The > 140/80 mm Hg threshold for treatment of high-risk patients in the Canadian guidelines refers to automated blood pressure readings, which are lower than nonautomated readings.
[4]Recommendations for persons > 75 years are not explicitly stated in the Hypertension Canada guidelines. They removed separate goals for the elderly but consider age > 75 years to be a risk signifier triggering an approach that many would view as overly aggressive in the extremely old.
[5]The European guidelines indicate a slightly more conservative treatment threshold of > 160/90 mm Hg for those > 80 years.
[6]This target range is also suggested in the European guidelines for patients > 80 years.
ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; ESH, European Society of Hypertension.

Table 11–5. Cardiovascular risk factors.

Major risk factors
Hypertension[1]
Cigarette smoking
Obesity (BMI ≥ 30)[1]
Physical inactivity
Dyslipidemia[1]
Diabetes mellitus[1]
Microalbuminuria or estimated GFR < 60 mL/minute/1.73 m^2
Age (> 55 years for men, > 65 years for women)
Family history of premature cardiovascular disease (< 55 years for men, < 65 years for women)
Target-organ damage
Heart
LVH
Angina or prior MI
Prior coronary revascularization
Heart failure
Brain
Stroke or transient ischemic attack
CKD
Peripheral arterial disease
Retinopathy

[1]Components of the metabolic syndrome.
Data from Chobanian AV et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289:2560.

Goals of Treatment

Traditionally, the most widely accepted goal for blood pressure management has been less than 140/90 mm Hg. However, observational studies suggest that there does not seem to be a blood pressure level below which decrements in cardiovascular risk taper off, and a number of randomized controlled trials have suggested that treatment to blood pressure targets considerably below 140 mm Hg may benefit certain patient groups.

The SPRINT study suggests that outcomes improve in nondiabetic patients with considerably elevated cardiovascular risk when treatment lowers systolic pressure to less than 120 mm Hg compared to less than 140 mm Hg. On the other hand, in the HOPE3 study of largely nondiabetic patients at somewhat lower risk than those in SPRINT, reducing blood pressure by an average of 6/3 mm Hg systolic/diastolic from a baseline of 138/82 mm Hg provided no significant outcomes benefits. Therefore, it appears that blood pressure targets should be lower in people at greater estimated cardiovascular risk. In response to the SPRINT study, the 2018 HC guidelines urge prescribers to consider a blood pressure goal of less than 120/80 mm Hg in patients considered at elevated risk for cardiovascular events. The 2017 ACC/AHA guidelines take a different approach by defining a 130/80 mm Hg goal as "reasonable" in nonelevated risk hypertensive patients, strengthening this to "recommended" in elevated risk hypertensive patients.

The 2018 ESH/ESC guidelines specify a target of less than 140 mm Hg systolic for all, and less than 130 mm Hg for most if tolerated. There is a trend toward recommending similar treatment targets in the elderly; this topic is discussed in greater detail below. Some experts note that manual office measurements of around 130/80 mm Hg are likely to approximate the lower blood pressure targets specified in the SPRINT study, which used automated office blood pressure measuring devices that have been demonstrated to read as much as 16/7 mm Hg lower than manual office readings. The 2018 Canadian guidelines acknowledge this disparity in measurement methods by specifying that automated office devices should be used in the monitoring of patients selected for the aggressive blood pressure goal of less than 120/80 mm Hg. Table 11–4 compares the treatment threshold and target recommendations laid out in the American, Canadian, and European guidelines.

Treatment to blood pressures less than 130 mm Hg systolic seems especially important in stroke prevention. The ACCORD study examined the effect of treatment of systolic pressures to below 130–135 mm Hg in patients with diabetes; the study's two by two factorial design addressed glycemic control as well as blood pressure control. In the original analysis, the lower blood pressure treatment goal significantly increased the risk of serious adverse effects (with no additional gain in terms of heart, kidney, or retinal disease). There was, however, significant additional reduction in the risk of stroke, indicating that lower blood pressure targets might be justified in diabetic patients at high risk for cerebrovascular events. Post hoc analysis of the ACCORD study after 9 years of follow-up suggested that a beneficial effect of lower blood pressure in older high-risk persons (mostly on nonfatal myocardial infarctions) could be detected in the standard glycemic control group. Similarly, in the SPS3 trial in patients who have had a lacunar stroke, treating the systolic blood pressure to less than 130 mm Hg (mean systolic blood pressure of 127 mm Hg among treated versus mean systolic blood pressure 138 mm Hg among untreated patients) probably reduced the risk of recurrent stroke (and with an acceptably low rate of adverse effects from treatment). Blood pressure management in acute stroke is discussed below.

How Low to Go?

Although observational studies indicate that the blood pressure–risk relationship holds up at levels considerably below 120 mm Hg, there has been uncertainty about whether this is true for treated blood pressure. This question was addressed in a secondary analysis of data from the ONTARGET and TRANSCEND studies in which participants with elevated cardiovascular risk but no history of stroke were treated with telmisartan (plus or minus ramipril) or placebo. The risk of the composite cardiovascular endpoint was lowest at a treated systolic blood pressure range between 120 mm Hg and 140 mm Hg. Increased risk was observed at blood pressures below and above this range. The risk of stroke was the only exception, with incremental benefit observed below a treated systolic of 120 mm Hg. With respect to diastolic blood pressure on treatment, composite risk began to increase at levels below 70 mm Hg. This suggests that the blood pressure–cardiovascular risk relationship evident in observational studies of untreated hypertension may not hold in the case of treated blood pressure and that there are grounds for a degree of caution in treating below a systolic pressure of 120 mm Hg.

In seeking to simplify decision making in the treatment of hypertension, some authors have suggested that a systolic blood pressure goal in the 120–130 mm Hg range would be safe and effective in high-risk patients, and a systolic blood pressure of around 130 mm Hg would be reasonable in lower-risk patients, irrespective of diastolic pressures. Diastolic blood pressure will track with systolic blood pressure; the main concern about diastolic blood pressure is that treatment will lower it too much in patients who have wider pulse pressures. However, it seems that a lower diastolic blood pressure as a consequence of treatment does not negate the benefits of systolic blood pressure control, even though wider pulse pressures at baseline are associated with cardiovascular mortality.

Treatment of Other Cardiovascular Risk Factors

Data from multiple studies indicate that statins should be part of the strategy to reduce overall cardiovascular risk. The HOPE3 study of persons at intermediate cardiovascular risk showed that 10 mg of rosuvastatin reduced average LDL cholesterol from 130 mg/dL to 90 mg/dL (3.36–2.33 mmol/L), and significantly reduced the risk of multiple cardiovascular events, including MI and coronary revascularization. Low-dose aspirin (81 mg/day) is no longer recommended in the primary prevention of MI or stroke. Low-dose aspirin is effective in prevention of recurrent cardiovascular events, but blood pressure should first be controlled to minimize the risk of cerebral hemorrhage.

Sheppard JP et al. Benefits and harms of antihypertensive treatment in low-risk patients with mild hypertension. JAMA Intern Med. 2018;178:1626. [PMID: 30383082]

Visseren FLJ et al; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol. 2022;29:5. [PMID: 34558602]

DRUG THERAPY: CURRENT ANTIHYPERTENSIVE AGENTS

There are many classes of antihypertensive drugs of which six (ACE inhibitors, ARBs, renin inhibitors, calcium channel blockers, diuretics, and beta-blockers) are suitable for initial therapy based on efficacy and tolerability. The specific classes of antihypertensive medications are discussed below, and guidelines for the choice of initial medications are offered.

A. Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors are commonly used as the initial medication in mild to moderate hypertension (Table 11–6). Their primary mode of action is inhibition of the RAAS, but they

Table 11–6. Antihypertensive drugs: renin and ACE inhibitors and ARBs.

Medication (Proprietary Name)	Oral Dosage	Cost of 30 Days of Treatment (Average Dosage)[1]	Adverse Effects	Comments
Renin Inhibitors				
Aliskiren (Tekturna)	*Initial:* 150 mg once daily *Range:* 150–300 mg once daily	$234.40 (150 mg)	Angioedema, hypotension, hyperkalemia. Contraindicated in pregnancy.	Probably metabolized by CYP3A4. Absorption is inhibited by high-fat meal.
Aliskiren and HCTZ (Tekturna HCT)	*Initial:* 150 mg/12.5 mg once daily *Range:* 150 mg/12.5 mg–300 mg/25 mg once daily	$293.54 (150 mg/12.5 mg)		
ACE Inhibitors				
Benazepril (Lotensin)	*Initial:* 10 mg once daily *Range:* 5–40 mg in 1 or 2 doses	$28.50 (20 mg)	Cough, hypotension, dizziness, hyperkalemia, kidney dysfunction, angioedema; taste alteration and rash (may be more frequent with captopril); rarely, proteinuria, blood dyscrasia. Contraindicated in pregnancy.	More fosinopril is excreted by the liver in patients with kidney dysfunction (dose reduction may or may not be necessary). Captopril and lisinopril are active without metabolism. Captopril, enalapril, lisinopril, and quinapril are approved for heart failure.
Benazepril and HCTZ (Lotensin HCT)	*Initial:* 5 mg/6.25 mg once daily *Range:* 5 mg/6.25 mg–20 mg/25 mg	$32.10 (any dose)		
Benazepril and amlodipine (Lotrel)	*Initial:* 10 mg/2.5 mg once daily *Range:* 10 mg/2.5 mg–40 mg/10 mg	$99.60 (20 mg/10 mg)		
Captopril (Capoten)	*Initial:* 25 mg twice daily *Range:* 50–450 mg in 2 or 3 doses	$76.20 (25 mg)		
Captopril and HCTZ (Capozide)	*Initial:* 25 mg/15 mg twice daily *Range:* 25 mg/15 mg–50 mg/25 mg	$171.00 (25 mg/15 mg)		
Enalapril (Vasotec)	*Initial:* 5 mg once daily *Range:* 5–40 mg in 1 or 2 doses	$28.50 (20 mg)		
Enalapril and HCTZ (Vaseretic)	*Initial:* 5 mg/12.5 mg once daily *Range:* 5 mg/12.5 mg–10 mg/25 mg	$35.70 (10 mg/25 mg)		
Fosinopril (Monopril)	*Initial:* 10 mg once daily *Range:* 10–80 mg in 1 or 2 doses	$15.90 (20 mg)		
Fosinopril and HCTZ (Monopril-HCT)	*Initial:* 10 mg/12.5 mg once daily *Range:* 10 mg/12.5 mg–20 mg/12.5 mg	$44.40 (any dose)		

(*continued*)

Table 11–6. Antihypertensive drugs: renin and ACE inhibitors and ARBs. (continued)

Medication (Proprietary Name)	Oral Dosage	Cost of 30 Days of Treatment (Average Dosage)[1]	Adverse Effects	Comments
Lisinopril (Prinivil, Zestril)	*Initial:* 5–10 mg once daily *Range:* 5–40 mg once daily	$2.40 (20 mg)		
Lisinopril and HCTZ (Prinzide or Zestoretic)	*Initial:* 10 mg/12.5 mg once daily *Range:* 10 mg/12.5 mg–20 mg/12.5 mg	$7.20 (20 mg/12.5 mg)		
Moexipril (Univasc)	*Initial:* 7.5 mg once daily *Range:* 7.5–30 mg in 1 or 2 doses	$41.70 (7.5 mg)		
Perindopril (Aceon)	*Initial:* 4 mg once daily *Range:* 4–16 mg in 1 or 2 doses	$84.00 (8 mg)		
Perindopril and amlodipine (Prestalia)	*Initial:* 3.5 mg/2.5 mg once daily *Range:* 3.5 mg/2.5–14 mg/10 mg once daily	$204.30 (7 mg/5 mg)		
Quinapril (Accupril)	*Initial:* 10 mg once daily *Range:* 10–80 mg in 1 or 2 doses	$36.60 (20 mg)		
Quinapril and HCTZ (Accuretic)	*Initial:* 10 mg/12.5 mg once daily *Range:* 10 mg/12.5 mg–20 mg/25 mg	$36.60 (20 mg/12.5 mg)		
Ramipril (Altace)	*Initial:* 2.5 mg once daily *Range:* 2.5–20 mg in 1 or 2 doses	$42.30 (5 mg)		
Trandolapril (Mavik)	*Initial:* 1 mg once daily *Range:* 1–8 mg once daily	$36.30 (4 mg)		
Trandolapril and verapamil (Tarka)	*Initial:* 2 mg/180 mg ER once daily *Range:* 2 mg/180 mg ER–8 mg/480 mg ER	$158.70 (any dose)		
ARBs				
Azilsartan (Edarbi)	*Initial:* 40 mg once daily *Range:* 40–80 mg once daily	$271.87 (80 mg)	Hyperkalemia, kidney dysfunction, rare angioedema. Combinations have additional side effects. Contraindicated in pregnancy.	Losartan has a flat dose-response curve. Valsartan and irbesartan have wider dose-response ranges and longer durations of action. Addition of low-dose diuretic (separately or as combination pills) increases the response.
Azilsartan and chlorthalidone (Edarbychlor)	*Initial:* 40 mg/12.5 mg once daily *Range:* 40 mg/12.5–40 mg/25 mg once daily	$256.62 (any dose)		
Candesartan cilexitil (Atacand)	*Initial:* 16 mg once daily *Range:* 8–32 mg once daily	$91.80 (16 mg)		
Candesartan cilexitil and HCTZ (Atacand HCT)	*Initial:* 16 mg/12.5 mg once daily *Range:* 32 mg/12.5 mg once daily	$141.60 (16 mg/12.5 mg)		
Eprosartan (Teveten)	*Initial:* 600 mg once daily *Range:* 400–800 mg in 1–2 doses	$102.78 (600 mg)		
Irbesartan (Avapro)	*Initial:* 150 mg once daily *Range:* 150–300 mg once daily	$13.80 (150 mg)		

Irbesartan and HCTZ (Avalide)	*Initial:* 150 mg/12.5 mg once daily *Range:* 150 mg/12.5 mg–300 mg/25 mg once daily	$20.10 (150 mg/12.5 mg)		
Losartan and HCTZ (Hyzaar)	*Initial:* 50 mg/12.5 mg once daily *Range:* 50 mg/12.5 mg–100 mg/25 mg once daily	$74.10 (50 mg/12.5 mg/)		
Olmesartan (Benicar)	*Initial:* 20 mg once daily *Range:* 20–40 mg once daily	$188.40 (20 mg)		
Olmesartan and HCTZ (Benicar HCT)	*Initial:* 20 mg/12.5 mg once daily *Range:* 20 mg/12.5 mg–40 mg/25 mg once daily	$188.40 (20 mg/12.5 mg)		
Olmesartan and amlodipine (Azor)	*Initial:* 20 mg/5 mg once daily *Range:* 20 mg/5 mg–40 mg/10 mg	$234.90 (20 mg/5 mg)		
Olmesartan and amlodipine and HCTZ (Tribenzor)	*Initial:* 20 mg/5 mg/12.5 mg once daily *Range:* 20 mg/5 mg/12.5 mg–40 mg/10 mg/25 mg once daily	$235.20 (20 mg/5 mg/12.5 mg)		
Telmisartan (Micardis)	*Initial:* 40 mg once daily *Range:* 20–80 mg once daily	$130.20 (40 mg)		
Telmisartan and HCTZ (Micardis HCT)	*Initial:* 40 mg/12.5 mg once daily *Range:* 40 mg/12.5 mg–80 mg/25 mg once daily	$144.90 (40 mg/12.5 mg)		
Telmisartan and amlodipine (Twynsta)	*Initial:* 40 mg/5 mg once daily *Range:* 40 mg/5 mg–80 mg/10 mg once daily	$171.30 (any dose)		
Valsartan (Diovan)	*Initial:* 80 mg once daily *Range:* 80 mg/12.5 mg–320 mg/25 mg once daily	$16.50 (160 mg)		
Valsartan and HCTZ (Diovan HCT)	*Initial:* 80 mg/12.5 mg once daily *Range:* 80–320 mg valsartan once daily	$128.10 (160 mg/12.5 mg)		
Valsartan and amlodipine (Exforge)	*Initial:* 160 mg/5 mg once daily *Range:* 160 mg/5 mg–320 mg/10 mg once daily	$186.00 (160 mg/10 mg)		
Other Combination Products				
Amlodipine and valsartan and HCTZ (Exforge HCT)	*Initial:* 5 mg/160 mg/12.5 mg once daily *Range:* 5 mg/160 mg/12.5 mg–10 mg/320 mg/25 mg once daily	$171.00 (160 mg valsartan)		

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.
Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at https://www.micromedexsolutions.com, accessed March 16, 2022. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.
ER, extended release; HCTZ, hydrochlorothiazide.

also inhibit bradykinin degradation, stimulate the synthesis of vasodilating prostaglandins, and can reduce sympathetic nervous system activity. ACE inhibitors appear to be more effective in younger White patients. They are relatively less effective in Black and older persons and in predominantly systolic hypertension. Although as single therapy they achieve adequate antihypertensive control in only about 40–50% of patients, the combination of an ACE inhibitor and a diuretic or calcium channel blocker is potent.

ACE inhibitors are the agents of choice in persons with type 1 diabetes with frank proteinuria or evidence of kidney dysfunction because they delay the progression to ESKD. Many authorities have expanded this indication to include persons with type 1 and type 2 diabetes mellitus with microalbuminuria who do not meet the usual criteria for antihypertensive therapy. ACE inhibitors may also delay the progression of nondiabetic kidney disease. The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that the ACE inhibitor ramipril reduced the number of cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes and also reduced the incidence of new-onset heart failure, kidney dysfunction, and new-onset diabetes in a population of patients at high risk for vascular events. Although this was not specifically a hypertensive population, the benefits were associated with a modest reduction in blood pressure, and the results inferentially support the use of ACE inhibitors in similar hypertensive patients. ACE inhibitors are a drug of choice (usually in conjunction with a diuretic and a beta-blocker) in patients with heart failure with reduced ejection fraction and are indicated also in asymptomatic patients with reduced ejection fraction.

How to initiate therapy—A baseline metabolic panel should be drawn prior to starting medications that interfere with the RAAS, repeated 1–2 weeks after initiation of therapy to evaluate changes in creatinine and potassium. Minor dose adjustments of these medications rarely trigger significant shifts in these values.

Side effects—An advantage of the ACE inhibitors is their relative freedom from troublesome side effects (Table 11–6). Severe hypotension can occur in patients with bilateral renal artery stenosis; significant increases in creatinine may ensue but are usually reversible with the discontinuation of the ACE inhibitor. Hyperkalemia may develop in patients with kidney disease and type IV renal tubular acidosis (commonly seen in patients with diabetes) and in older adults. A chronic dry cough is common, seen in 10% of patients or more, and may require stopping the drug. Skin rashes are observed with any ACE inhibitor. Angioedema is an uncommon but potentially dangerous side effect of all agents of this class because of their inhibition of kininase. Exposure of the fetus to ACE inhibitors during the second and third trimesters of pregnancy has been associated with a variety of defects due to hypotension and reduced renal blood flow.

B. Angiotensin II Receptor Blockers

ARBs can improve cardiovascular outcomes in patients with hypertension as well as in patients with related conditions, such as heart failure and type 2 diabetes with nephropathy. ARBs have not been compared with ACE inhibitors in randomized controlled trials in patients with hypertension, but two trials comparing losartan with captopril in heart failure and post–MI LV dysfunction showed trends toward worse outcomes in the losartan group. By contrast, valsartan seems as effective as ACE inhibitors in these settings. Within group heterogeneity of antihypertensive potency and duration of action might explain such observations. The Losartan Intervention for Endpoints (LIFE) trial in nearly 9000 hypertensive patients with electrocardiographic evidence of LVH—comparing losartan with the beta-blocker atenolol as initial therapy—demonstrated a significant reduction in stroke with losartan. Of note is that in diabetic patients, death and MI were also reduced, and there was a lower occurrence of new-onset diabetes. In a subgroup analysis from the LIFE trial, atenolol appeared to be superior to losartan in African Americans, while the opposite was the case in non-African Americans. A similar reduced efficacy of lisinopril compared to diuretics and calcium channel blockers was observed in Black persons in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attach Trial (ALLHAT), suggesting that ACE inhibitors and ARBs may not be the preferred agents in Black patients (see Table 11–12). In the treatment of hypertension, combination therapy with an ACE inhibitor and an ARB is not advised because it generally offers no advantage over monotherapy at maximum dose with addition of a complementary class where necessary.

Side effects—Unlike ACE inhibitors, the ARBs rarely cause cough and are less likely to be associated with skin rashes or angioedema (Table 11–6). However, as seen with ACE inhibitors, hyperkalemia can be a problem, and patients with bilateral renal artery stenosis may exhibit hypotension and worsened kidney function. Olmesartan has been linked to a sprue-like syndrome, presenting with abdominal pain, weight loss, and nausea, which subsides upon drug discontinuation. There is evidence from an observational study suggesting that ARBs and ACE inhibitors are less likely to be associated with depression than calcium channel blockers and beta-blockers.

C. Renin Inhibitors

Since renin cleavage of angiotensinogen is the rate-limiting step in the renin-angiotensin cascade, the most efficient inactivation of this system would be expected with renin inhibition. Conventional ACE inhibitors and ARBs probably offer incomplete blockade, even in combination. Aliskiren, a renin inhibitor, binds the proteolytic site of renin, thereby preventing cleavage of angiotensinogen. Aliskiren effectively lowers blood pressure, reduces albuminuria, and limits LVH, but it has yet to be established as a first-line drug based on outcomes data. The combination of aliskiren with ACE inhibitors or ARBs in persons with type 2 diabetes mellitus offers no advantage and might even increase the risk of adverse cardiac or renal consequences.

D. Calcium Channel Blocking Agents

These agents act by causing peripheral vasodilation but with less reflex tachycardia and fluid retention than other

vasodilators. They are effective as single-drug therapy in approximately 60% of patients in all demographic groups and all grades of hypertension (Table 11–7). For these reasons, they may be preferable to beta-blockers and ACE inhibitors in Black and older persons. Verapamil and diltiazem should be combined cautiously with beta-blockers because of their potential for depressing atrioventricular (AV) conduction and sinus node automaticity as well as contractility.

Calcium channel blockers are equivalent to ACE inhibitors and thiazide diuretics in prevention of CHD, major cardiovascular events, cardiovascular death, and total mortality. A protective effect against stroke with calcium channel blockers is well established, and in two trials (ALLHAT and the Systolic Hypertension in Europe trial), these agents appeared to be more effective than diuretic-based therapy.

Side effects—The most common side effects of calcium channel blockers are headache, peripheral edema, bradycardia, and constipation (especially with verapamil in older adults) (Table 11–7). The dihydropyridine agents—nifedipine, nicardipine, isradipine, felodipine, nisoldipine, and amlodipine—are more likely to produce symptoms of vasodilation, such as headache, flushing, palpitations, and peripheral edema. Edema is minimized by coadministration of an ACE inhibitor or ARB. Calcium channel blockers have negative inotropic effects and should be used cautiously in patients with cardiac dysfunction. Amlodipine is the only calcium channel blocker with established safety in patients with severe heart failure.

E. Diuretics

Thiazide diuretics (Table 11–8) are the antihypertensives that have been most extensively studied and most consistently effective in clinical trials. They lower blood pressure initially by decreasing plasma volume, but during long-term therapy, their major hemodynamic effect is reduction of peripheral vascular resistance. Most of the antihypertensive effect of these agents is achieved at lower dosages (typically, 12.5 mg of hydrochlorothiazide or equivalent), but their biochemical and metabolic effects are dose related. Chlorthalidone has the advantage of better 24-hour blood pressure control than hydrochlorothiazide in clinical trials. Thiazides may be used at higher doses if plasma potassium is above 4.5 mmol/L. The loop diuretics (such as furosemide) may lead to electrolyte and volume depletion more readily than the thiazides and have short durations of action. Because of these adverse effects, loop diuretics should be reserved for use in patients with kidney dysfunction (serum creatinine greater than 2.5 mg/dL [208.3 mcmol/L]; estimated eGFR less than 30 mL/minute/1.73 m^2) in which case they are more effective than thiazides. Relative to beta-blockers and ACE inhibitors, diuretics are more potent in Black persons, older individuals, obese persons, and other subgroups with increased plasma volume or low plasma renin activity (or both). They are relatively more effective in cigarette smokers than in nonsmokers. Long-term thiazide administration also mitigates the loss of bone mineral content in older women at risk for osteoporosis.

Overall, diuretics administered alone control blood pressure in 50% of patients with mild to moderate hypertension and can be used effectively in combination with all other agents. They are also useful for lowering isolated or predominantly systolic hypertension.

Side effects—The adverse effects of diuretics relate primarily to the metabolic changes listed in Table 11–8. Erectile dysfunction, skin rashes, and photosensitivity are less frequent. Hypokalemia has been a concern but is uncommon at the recommended dosages. The risk can be minimized by limiting dietary salt or increasing dietary potassium; potassium replacement is not usually required to maintain serum K^+ at greater than 3.5 mmol/L. Higher serum K^+ levels are prudent in patients at special risk from intracellular potassium depletion, such as those taking digoxin or with a history of ventricular arrhythmias, in which case a potassium-sparing agent could be used. Compared with ACE inhibitors and ARBs, diuretic therapy is associated with a slightly higher incidence of mild new-onset diabetes. Diuretics also increase serum uric acid and may precipitate gout. Increases in blood glucose, triglycerides, and LDL cholesterol may occur but are relatively minor during long-term low-dose therapy. The potential for worsening of diabetes is outweighed by the advantages of blood pressure control, and diuretics should not be withheld from diabetic patients.

F. Aldosterone Receptor Antagonists

Spironolactone and eplerenone are natriuretic in sodium-retaining states, such as heart failure and cirrhosis, but only very weakly so in hypertension. These drugs have reemerged in the treatment of hypertension, particularly in resistant patients and are helpful additions to most other antihypertensive medications. Consistent with the increasingly appreciated importance of aldosterone in essential hypertension, the aldosterone receptor blockers are effective at lowering blood pressure in all hypertensive patients regardless of renin level and are also effective in Black persons. Aldosterone plays a central role in target-organ damage, including the development of ventricular and vascular hypertrophy and renal fibrosis. Aldosterone receptor antagonists ameliorate these consequences of hypertension, to some extent independently of effects on blood pressure.

Side effects—Spironolactone can cause breast pain and gynecomastia in men through activity at the progesterone receptor, an effect not seen with the more specific eplerenone. Hyperkalemia is a problem with both drugs, chiefly in patients with CKD. Hyperkalemia is more likely if the pretreatment plasma potassium exceeds 4.5 mmol/L.

G. Beta-Blocking Agents

These drugs are effective in hypertension because they decrease the heart rate and cardiac output. The beta-blockers also decrease renin release and are more efficacious in populations with elevated plasma renin activity, such as younger White patients. They neutralize the reflex tachycardia caused by vasodilators and are especially useful in patients with associated conditions that benefit from the

Table 11–7. Antihypertensive drugs: calcium channel blocking agents.

Medication (Proprietary Name)	Oral Dosages	Cost of 30 Days of Treatment (Average Dosage)[1]	Special Properties			Adverse Effects	Comments
			Peripheral Vasodilation	Cardiac Automaticity and Conduction	Contractility		
Nondihydropyridine Agents							
Diltiazem							
(Cardizem SR)	*Initial:* 90 mg twice daily *Range:* 180–360 mg in 2 doses	$283.80 (120 mg twice daily)	++	↓↓	↓↓	Edema, headache, bradycardia, bloating and constipation, dizziness, AV block, heart failure, urinary frequency.	Also approved for angina.
(Cardizem CD)	*Initial:* 180 mg ER once daily *Range:* 180–360 mg ER once daily	$42.00 (240 mg once daily)					
(Cartia XT)	*Initial:* 180 or 240 mg ER once daily *Range:* 180–480 mg ER once daily	$42.00 (240 mg once daily)					
Dilt-XR	*Initial:* 180 or 240 mg ER once daily *Range:* 180–540 mg ER once daily	$42.90 (240 mg once daily)					
(Taztia XT)	*Initial:* 120 or 180 mg ER once daily *Range:* 120–540 mg ER once daily	$53.40 (240 mg once daily)					
(Tiazac)	*Initial:* 120 or 240 mg ER once daily *Range:* 120–540 mg ER once daily	$53.40 (240 mg once daily)					
Verapamil							
(Calan)	*Initial:* 40 mg three times daily *Range:* 120–480 mg in 3 divided doses	$35.10 (80 mg three times daily)	++	↓↓↓	↓↓↓	Same as diltiazem but more likely to cause constipation and heart failure.	Also approved for angina and arrhythmias.
(Calan SR)	*Initial:* 120 mg ER once daily *Range:* 120–480 mg ER in 1 or 2 doses	$49.20 (240 mg once daily)					
(Verelan)	*Initial:* 120 or 240 mg ER once daily *Range:* 240–480 mg ER once daily	$68.70 (240 mg once daily)					
(Verelan PM)	*Initial:* 100 or 200 mg ER once daily *Range:* 100–400 mg ER once daily	$75.90 (200 mg once daily)					

Dihydropyridines							
Amlodipine (Norvasc)	*Initial:* 2.5 mg once daily *Range:* 2.5–10 mg once daily	$3.00 (10 mg once daily)	+++	↓/0	↓/0	Edema, dizziness, palpitations, flushing, headache, hypotension, tachycardia, bloating and constipation, urinary frequency.	Amlodipine, nicardipine, and nifedipine also approved for angina.
Amlodipine and atorvastatin (Caduet)	*Initial:* 2.5 mg/10 mg once daily *Range:* 10 mg/80 mg once daily	$281.10 (10 mg/40 mg daily)	+++	↓/0	↓/0	Edema (amlodipine), myopathy and hepatotoxicity (atorvastatin).	
Felodipine (Plendil)	*Initial:* 5 mg ER once daily *Range:* 5–10 mg ER once daily	$65.40 (10 mg ER daily)	+++	↓/0	↓/0		
Isradipine (DynaCirc)	*Initial:* 2.5 mg twice daily *Range:* 2.5–5 mg twice daily	$225.60 (5 mg twice daily)	+++	↓/0	↓		
Nicardipine (Cardene)	*Initial:* 20 mg three times daily *Range:* 20–40 mg three times daily	$200.70 (20 mg three times daily)	+++	↓/0	↓		
Nifedipine (Adalat CC)	*Initial:* 30 mg ER once daily *Range:* 30–90 mg ER once daily	$68.70/60 mg daily	+++	↓	↓↓		
Nifedipine (Procardia XL)	*Initial:* 30 or 60 mg ER once daily *Range:* 30–120 mg ER once daily	$19.80/60 mg daily					
Nisoldipine (Sular)	*Initial:* 17 mg daily *Range:* 17–34 mg daily	$251.70 (34 mg once daily)	+++	↓/0	↓		

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.
Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at https://www.micromedexsolutions.com, accessed March 16, 2022. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.
AV, atrioventricular; ER, extended release.

Table 11–8. Antihypertensive drugs: diuretics (in descending order of preference).

Drugs	Proprietary Names	Oral Doses	Cost of 30 Days of Treatment[1] (Average Dosage)	Adverse Effects	Comments
Thiazides and Related Diuretics					
Hydrochlorothiazide (HCTZ)	Esidrix, Microzide	*Initial:* 12.5 or 25 mg once daily *Range:* 12.5–50 mg once daily	$2.40 (25 mg)	↓K^+, ↓Mg^{2+}, ↑Ca^{2+}, ↓Na+, ↑uric acid, ↑glucose, ↑LDL cholesterol, ↑triglycerides; rash, erectile dysfunction.	Low dosages effective in many patients without associated metabolic abnormalities
Chlorthalidone	Thalitone	*Initial:* 12.5 or 25 mg once daily *Range:* 12.5–50 mg once daily	$36.30 (25 mg)		Better 24-hour blood pressure control than HCTZ because of longer half-life
Metolazone	Zaroxolyn	*Initial:* 1.25 or 2.5 mg once daily *Range:* 1.25–5 mg once daily	$70.80 (5 mg)		More effective with concurrent kidney disease
Indapamide	Lozol	*Initial:* 2.5 mg once daily *Range:* 2.5–5 mg once daily	$30.60 (2.5 mg)		Does not alter serum lipid levels
Bendroflumethiazide	Aprinox Neo-Naclex	*Initial:* 2.5 mg once daily	—		Not available in United States
Loop Diuretics					
Furosemide	Lasix	*Initial:* 20 mg twice daily *Range:* 40–320 mg in 2 or 3 doses	$5.40 (40 mg)	Same as thiazides, but with higher risk of excessive diuresis and electrolyte imbalance. Increases calcium excretion.	Short duration of action a disadvantage; should be reserved for patients with kidney disease or fluid retention. Poor antihypertensive.
Ethacrynic acid	Edecrin	*Initial:* 50 mg once daily *Range:* 50–100 mg once or twice daily	$1437.00 (25 mg)		
Bumetanide	(generic)	*Initial:* 0.25 mg twice daily *Range:* 0.5–10 mg in 2 or 3 doses	$32.40 (1 mg)		
Torsemide	Demadex	*Initial:* 5 mg once daily *Range:* 5–10 mg once daily	$21.00 (10 mg)		Effective blood pressure medication at low dosage.
Aldosterone Receptor Blockers					
Spironolactone	Aldactone	*Initial:* 12.5 or 25 mg once daily *Range:* 12.5–100 mg once daily	$5.70 (25 mg)	Hyperkalemia, metabolic acidosis, gynecomastia.	Can be useful add-on therapy in patients with refractory hypertension.
Amiloride	(generic)	*Initial:* 5 mg once daily *Range:* 5–10 mg once daily	$6.90 (5 mg)		
Eplerenone	Inspra	*Initial:* 25 mg once daily *Range:* 25–100 mg once daily	$123.00 (25 mg)		

Combination Products					
HCTZ and triamterene	Dyazide, Maxzide-25 (25/37.5 mg)	*IInitial:* 25 mg/37.5 mg once daily *Range*: 25 mg/37.5 mg–50 mg/75 mg once daily	$10.80	Same as thiazides plus GI disturbances, hyperkalemia rather than hypokalemia, headache; triamterene can cause kidney stones and kidney dysfunction; spironolactone causes gynecomastia. Hyperkalemia can occur if this combination is used in patients with advanced kidney disease or those taking ACE inhibitors.	Use should be limited to patients with demonstrable need for a potassium-sparing agent.
HCTZ and amiloride	(generic) (50/5 mg)	*Initial:* 25 mg/2.5 mg once daily *Range:* 50 mg/5 mg–100 mg/10 mg once daily	$34.80		
HCTZ and spironolactone	Aldactazide (25/25 mg; 50/50 mg)	*Initial:* 25 mg/25 mg once daily *Range:* 25 mg/25 mg–100 mg/100 mg once daily	$37.20 (25/25 mg)		

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.
Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at https://www.micromedexsolutions.com, accessed March 16, 2022. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

cardioprotective effects of these agents. These include individuals with angina pectoris, previous myocardial infarction, and stable heart failure as well as those with migraine headaches and somatic manifestations of anxiety.

Although all beta-blockers appear to be similar in antihypertensive potency, they differ in a number of pharmacologic properties (these differences are summarized in Table 11–9), including specificity to the cardiac beta-1-receptors (cardioselectivity) and whether they also block the beta-2-receptors in the bronchi and vasculature*; at higher dosages, however, all agents are nonselective.* The beta-blockers also differ in their pharmacokinetics, lipid solubility—which determines whether they cross the blood-brain barrier predisposing to CNS side effects—and route of metabolism. Metoprolol reduces mortality and morbidity in patients with chronic stable heart failure with reduced ejection fraction (see Chapter 10). Carvedilol and nebivolol maintain cardiac output and are beneficial in patients with LV systolic dysfunction. Carvedilol and nebivolol may reduce peripheral vascular resistance by concomitant alpha-blockade (carvedilol) and increased nitric oxide release (nebivolol). Because of the lack of efficacy in primary prevention of MI and inferiority compared with other drugs in prevention of stroke and LVH, traditional beta-blockers should not be used as first-line agents in the treatment of hypertension without specific compelling indications (such as active CAD). Vasodilating beta-blockers may emerge as alternative first-line antihypertensives, but this possibility has yet to be rigorously tested in outcome studies.

Side effects—The side effects of beta-blockers include inducing or exacerbating bronchospasm in predisposed patients; sinus node dysfunction and AV conduction depression (resulting in bradycardia or AV block); nasal congestion; Raynaud phenomenon; and CNS symptoms with nightmares, excitement, depression, and confusion. Fatigue, lethargy, and erectile dysfunction may occur. The traditional beta-blockers (but not the vasodilator beta-blockers carvedilol and nebivolol) have an adverse effect on lipids and glucose metabolism. Beta-blockers are used cautiously in patients with type 1 diabetes since they can mask the symptoms of hypoglycemia and prolong these episodes by inhibiting gluconeogenesis. These drugs should also be used with caution in patients with advanced peripheral vascular disease associated with rest pain or nonhealing ulcers, but they are generally well tolerated in patients with mild claudication. Nebivolol can be safely used in patients with stage II claudication (claudication at 200 m).

In treatment of pheochromocytoma, beta-blockers should not be administered until alpha-blockade (eg, phentolamine) has been established. Otherwise, blockade of vasodilatory beta-2-adrenergic receptors will allow unopposed vasoconstrictor alpha-adrenergic–receptor activation with worsening of hypertension. *For the same reason, beta-blockers should not be used to treat hypertension arising from cocaine use.*

Great care should be exercised if the decision is made, in the absence of compelling indications, to remove beta-blockers from the treatment regimen because abrupt withdrawal can precipitate acute coronary events and severe increases in blood pressure.

H. Alpha-Antagonists

Prazosin, terazosin, and doxazosin (Table 11–10) block postsynaptic alpha-receptors, relax smooth muscle, and reduce blood pressure by lowering peripheral vascular resistance. These agents are effective as single-drug therapy in some individuals, but tachyphylaxis may appear during long-term therapy. Unlike beta-blockers and diuretics, alpha-blockers have no adverse effect on serum lipid levels. In fact, alpha-blockers increase HDL cholesterol while reducing total cholesterol; whether this is beneficial in the long term has not been established.

Side effects—Side effects are relatively common (Table 11–10). These include marked hypotension after the first dose which, therefore, should be small and given at bedtime. Post-dosing palpitations, headache, and nervousness may continue to occur during long-term therapy; these symptoms may be less frequent or severe with doxazosin because of its more gradual onset of action. In ALLHAT, persons receiving doxazosin as initial therapy had a significant increase in heart failure hospitalizations and a higher incidence of stroke relative to those receiving diuretics, prompting discontinuation of this arm of the study. Cataractectomy in patients exposed to alpha-blockers can be complicated by the floppy iris syndrome, even after discontinuation of the drug, so the ophthalmologist should be alerted that the patient has been taking the drug prior to surgery.

To summarize, alpha-blockers should generally not be used as initial agents to treat hypertension—except perhaps in men with symptomatic prostatism or nightmares linked to PTSD.

I. Drugs With Central Sympatholytic Action

Methyldopa, clonidine, guanabenz, and guanfacine (Table 11–10) lower blood pressure by stimulating alpha-adrenergic receptors in the CNS, thus reducing efferent peripheral sympathetic outflow. There is considerable experience with methyldopa in pregnant women, and it is still used for this population. Clonidine is available in patches, which may have particular value in noncompliant patients. All of these central sympatholytic agents are effective as single therapy in some patients, but they are usually used as second- or third-line agents because of the high frequency of drug intolerance.

Side effects—Side effects include sedation, fatigue, dry mouth, postural hypotension, and erectile dysfunction. An important concern is rebound hypertension following withdrawal. Methyldopa also causes hepatitis and hemolytic anemia and should be restricted to individuals who have already tolerated long-term therapy.

J. Peripheral Sympathetic Inhibitors

These agents are usually used only in refractory hypertension. Reserpine remains a cost-effective antihypertensive agent (Table 11–10). Its reputation for inducing mental depression and its other side effects—sedation, nasal stuffiness, sleep disturbances, and peptic ulcers—has made it unpopular, though these problems are uncommon at low dosages. Guanethidine and guanadrel inhibit catecholamine

Table 11–9. Antihypertensive drugs: beta-blocking agents.

Medication (Proprietary Name)	Oral Dosage	Cost of 30 Days of Treatment (Average Dosage)[1]	Special Properties					Comments[5]
			Beta-1 Selectivity[2]	ISA[3]	MSA[4]	Lipid Solubility	Renal vs Hepatic Elimination	
Acebutolol (Sectral)	*Initial:* 400 mg once daily *Range:* 200–1200 mg in 1 or 2 doses	$47.10 (400 mg)	+	+	+	+	H > R	Positive ANA; rare LE syndrome; also indicated for arrhythmias. Doses > 800 mg have beta-1 and beta-2 effects.
Atenolol (Tenormin)	*Initial:* 25 mg once daily *Range:* 25–100 mg once daily	$24.90 (50 mg)	+	0	0	0	R	Also indicated for angina and post-MI. Doses > 100 mg have beta-1 and beta-2 effects.
Atenolol/chlorthalidone (Tenoretic)	*Initial:* 50 mg/25 mg once daily *Range:* 50 mg/25 mg–100 mg/25 mg once daily	$56.40 (50 mg/25 mg)	+	0	0	0	R	
Betaxolol (Kerlone)	*Initial:* 10 mg once daily *Range:* 10–40 mg once daily	$36.90 (10 mg)	+	0	0	+	H > R	
Bisoprolol (Zebeta)	*Initial:* 5 mg once daily *Range:* 5–20 mg once daily	$42.00 (10 mg)	+	0	0	0	R = H	Also effective for heart failure.
Bisoprolol and HCTZ (Ziac)	*Initial:* 2.5 mg/6.25 mg once daily *Range:* 2.5 mg/6.25 mg–10 mg/6.25 mg once daily	$101.10 (2.5/6.25 mg)	+	0	0	0	R = H	Low-dose combination approved for initial therapy.
Carvedilol (Coreg)	*Initial:* 6.25 mg twice daily *Range:* 12.5–50 mg in 2 doses	$5.40 (25 mg)	0	0	0	+++	H > R	Alpha:beta blocking activity 1:9; may cause orthostatic symptoms; effective for heart failure. Nitric oxide potentiating vasodilatory activity.[6]
Carvedilol (Coreg CR)	*Initial:* 20 mg ER once daily *Range:* 20–80 mg ER once daily	$297.30 (any tablet)	0	0	0	+++	H > R	
Labetalol (Trandate)	*Initial:* 100 mg twice daily *Range:* 200–2400 mg in 2 doses	$23.40 (200 mg)	0	0/+	0	++	H	Alpha:beta blocking activity 1:3; more orthostatic hypotension, fever, hepatotoxicity.
Metoprolol (Lopressor)	*Initial:* 50 mg twice daily *Range:* 50–200 mg twice daily	$7.80 (50 mg)	+	0	+	+++	H	Also indicated for angina and post-MI. Approved for heart failure. Doses > 100 mg have beta-1 and beta-2 effects.
Metoprolol (Toprol-XL [SR preparation])	*Initial:* 25 mg once daily *Range:* 25–400 mg once daily	$6.00 (100 mg)						

(*continued*)

Table 11–9. Antihypertensive drugs: beta-blocking agents. (continued)

Medication (Proprietary Name)	Oral Dosage	Cost of 30 Days of Treatment (Average Dosage)[1]	Special Properties					Comments[5]
			Beta-1 Selectivity[2]	ISA[3]	MSA[4]	Lipid Solubility	Renal vs Hepatic Elimination	
Metoprolol and HCTZ (Lopressor HCT)	*Initial:* 50 mg/12.5 mg twice daily *Range:* 50 mg/25 mg–200 mg/50 mg in single or divided doses	$131.40 (100 mg/25 mg)	+	0	+	+++	H	
Nadolol (Corgard)	*Initial:* 20 mg once daily *Range:* 20–320 mg once daily	$7.20 (40 mg)	0	0	0	0	R	
Nebivolol (Bystolic)	*Initial:* 5 mg once daily *Range:* 40 mg once daily	$100.80 (5 mg)	+	0	0	++	H	Nitric oxide potentiating vasodilatory activity.[6]
Pindolol (Visken)	*Initial:* 5 mg twice daily *Range:* 10–60 mg in 2 doses	$79.20 (5 mg)	0	++	+	+	H > R	In adults, 35% renal clearance
Propranolol								
(Inderal)	*Initial:* 20 mg twice daily *Range:* 40–640 mg in 2 doses	$18.60 (40 mg)	0	0	++	+++	H	Also indicated for angina and post-MI.
(Inderal LA)	*Initial:* 80 mg ER once daily *Range:* 120–640 mg ER once daily	$89.40 (120 mg)						
(InnoPran XL)	*Initial:* 80 mg ER once nightly *Range:* 80–120 mg ER once nightly	$906.00 (120 mg)						
Propranolol and HCTZ (generic)	*Initial:* 40 mg/25 mg twice daily *Range:* 40 mg/25 mg–80 mg/25 mg twice daily	$84.60 (80 mg/25 mg)	0	0	++	+++	H	
Timolol (generic)	*Initial:* 5 mg twice daily *Range:* 10–60 mg in 2 doses	$102.00 (10 mg)	0	0	0	++	H > R	Also indicated for post-MI; 80% hepatic clearance.

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.
Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at https://www.micromedexsolutions.com, accessed March 16, 2022. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.
[2]Agents with beta-1 selectivity are less likely to precipitate bronchospasm and decrease peripheral blood flow in low doses, but selectivity is only relative.
[3]Agents with ISA cause less resting bradycardia and lipid changes.
[4]MSA generally occurs at concentrations greater than those necessary for beta-blockade. The clinical importance of MSA by beta-blockers has not been defined.
[5]Adverse effects of all beta-blockers: bronchospasm, fatigue, sleep disturbance and nightmares, bradycardia and atrioventricular block, worsening of heart failure, cold extremities, GI disturbances, erectile dysfunction, ↑ triglycerides, ↓ HDL cholesterol, rare blood dyscrasias.
[6]Carvedilol and nebivolol stimulate release of nitric oxide by vascular endothelium, which may augment the vasodilatory effects of drugs such as hydralazine and prazosin.
ANA, antinuclear antibody; ER, extended release; HCTZ, hydrochlorothiazide; ISA, intrinsic sympathomimetic activity; LE, lupus erythematosus; MSA, membrane-stabilizing activity; SR, sustained release; 0, no effect; +, some effect; ++, moderate effect; +++, most effect.

Table 11–10. Alpha-blocking agents, sympatholytics, and vasodilators.

Medication (Proprietary Names)	Dosage	Cost of 30 Days of Treatment (Average Dosage)[1]	Adverse Effects	Comments
Alpha-Blockers				
Doxazosin (Cardura)	*Initial:* 1 mg at bedtime *Range:* 1–16 mg once daily	$8.70 (4 mg)	Syncope with first dose; postural hypotension, dizziness, palpitations, headache, weakness, drowsiness, sexual dysfunction, anticholinergic effects, urinary incontinence; first-dose effects may be less with doxazosin.	May ↑ HDL and ↓ LDL cholesterol. May provide short-term relief of obstructive prostatic symptoms. Less effective in preventing cardiovascular events than diuretics.
Doxazosin (Cardura XL)	*Initial:* 4 mg ER once daily *Range:* 4–8 mg ER once daily	$212.10 (4 mg ER)		
Prazosin (Minipress)	*Initial:* 1 mg at bedtime *Range:* 2–20 mg in 2 or 3 doses	$130.80 (5 mg)		
Terazosin (Hytrin)	*Initial:* 1 mg at bedtime *Range:* 1–20 mg in 1 or 2 doses	$48.30 (5 mg)		
Central Sympatholytics				
Clonidine (Catapres)	*Initial:* 0.1 mg twice daily *Range:* 0.2–0.6 mg in 2 doses	$3.00 (0.1 mg)	Sedation, dry mouth, sexual dysfunction, headache, bradyarrhythmias; side effects may be less with guanfacine. Contact dermatitis with clonidine patch.	"Rebound" hypertension may occur even after gradual withdrawal.
Clonidine (Catapres TTS [transdermal patch])	*Initial:* 0.1 mg/day patch weekly *Range:* 0.1–0.3 mg/day patch weekly	$223.06 (0.2 mg patch)		
Clonidine and chlorthalidone (Clorpres)	*Initial:* 0.1 mg/15 mg one to three times daily *Range:* 0.1 mg/15 mg–0.6 mg/30 mg in single or divided doses	$166.20 (0.1 mg/15 mg)		
Guanfacine (Tenex)	*Initial:* 1 mg once daily *Range:* 1–3 mg once daily	$26.10 (1 mg)		
Methyldopa (Aldochlor)	*Initial:* 250 mg twice daily *Range:* 500–2000 mg in 2 doses	$39.60 (500 mg)	Hepatitis, hemolytic anemia, fever.	Avoid in favor of safer agents.
Peripheral Neuronal Antagonists				
Reserpine (generic)	*Initial:* 0.05 mg once daily *Range:* 0.05–0.25 mg once daily	$35.70 (0.1 mg)	Depression (less likely at low dosages, ie, < 0.25 mg), night terrors, nasal stuffiness, drowsiness, peptic disease, GI disturbances, bradycardia.	
Direct Vasodilators				
Hydralazine (Apresoline)	*Initial:* 25 mg twice daily *Range:* 50–300 mg in 2–4 doses	$9.00 (25 mg)	GI disturbances, tachycardia, headache, nasal congestion, rash, LE-like syndrome.	May worsen or precipitate angina.
Minoxidil (generic)	*Initial:* 5 mg once daily *Range:* 10–40 mg once daily	$38.40 (10 mg)	Tachycardia, fluid retention, headache, hirsutism, pericardial effusion, thrombocytopenia.	Should be used in combination with beta-blocker and diuretic.

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.
Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at https://www.micromedexsolutions.com, accessed March 16, 2022. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.
ER, extended release; LE, lupus erythematosus.

release from peripheral neurons but frequently cause orthostatic hypotension (especially in the morning or after exercise), diarrhea, and fluid retention.

K. Arteriolar Dilators

Hydralazine and minoxidil (Table 11–10) relax vascular smooth muscle and produce peripheral vasodilation. When given alone, they stimulate reflex tachycardia; increase myocardial contractility; and cause headache, palpitations, and fluid retention. To counteract these effects, the agents are usually given in combination with diuretics and beta-blockers in resistant patients. Hydralazine produces frequent GI disturbances and may induce a lupus-like syndrome. Minoxidil causes hirsutism and marked fluid retention; this very potent agent is reserved for the most refractory of cases.

Antihypertensive Medications & the Risk of Cancer

A number of observational studies have examined the association between long-term exposure to antihypertensive medications and cancer. Weak associations have been suggested by some of these studies, but results have been mixed. In the absence of large-scale prospective studies with cancer as a prespecified outcome measure, the effect of antihypertensive drugs on the risk of cancer remains uncertain. By contrast, the beneficial effect of these drugs on cardiovascular outcomes has been clearly established. Concern about increased risk of cancer should not be minimized, but at present there are no compelling data to prompt a change in prescribing patterns.

Procedures That Modulate the Activity of the Autonomic Nervous System

Before the advent of antihypertensive medications, lumbar sympathectomy was used to lower blood pressure. In a more specific and less invasive approach, the renal sympathetic nerves can be ablated using radiofrequency energy applied to the luminal surface of the renal arteries. However, the Symplicity HTN-3 study of renal sympathetic denervation did not show any difference in blood pressure reduction compared to a sham procedure group. Subsequently, the SPYRAL HTN-OFF MED study, using a more intensive and closely controlled ablation strategy, demonstrated modest but clinically meaningful blood pressure reductions compared to the sham control group. This effect on blood pressure has been confirmed by several subsequent studies. Although not yet accepted in general clinical practice, it seems probable that renal sympathetic nerve ablation will emerge as an alternative or adjunctive modality in the treatment of hypertension and may have a role in the management of resistant hypertension and drug intolerance.

Developing an Antihypertensive Regimen

Historically, data from large placebo-controlled trials supported the overall conclusion that antihypertensive therapy with diuretics and beta-blockers had a major beneficial effect on a broad spectrum of cardiovascular outcomes, reducing the incidence of stroke by 30–50% and of heart failure by 40–50%, and halting progression to accelerated hypertension syndromes. The decreases in fatal and nonfatal CHD and cardiovascular and total mortality were less dramatic, ranging from 10% to 15%. Similar placebo-controlled data pertaining to the newer agents are generally lacking, except for stroke reduction with the calcium channel blocker nitrendipine in the Systolic Hypertension in Europe trial. However, there is substantial evidence that ACE inhibitors, and to a lesser extent ARBs, reduce adverse cardiovascular outcomes in other related populations (eg, patients with diabetic nephropathy, heart failure, or post-MI and individuals at high risk for cardiovascular events). Most large clinical trials that have compared outcomes in relatively unselected patients have failed to show a difference between newer agents—such as ACE inhibitors, calcium channel blockers, and ARBs—and the older diuretic-based regimens with regard to survival, myocardial infarction, and stroke. Where differences have been observed, they have mostly been attributable to subtle asymmetries in blood pressure control rather than to any inherent advantages of one agent over another. Recommendations for initial treatment identify ACE inhibitors, ARBs, and calcium channel blockers as valid choices. Because of their adverse metabolic profile, initial therapy with thiazides might best be restricted to older patients. Thiazides are acceptable as first-line therapy in Black persons because of specific efficacy in this group.

As discussed above, beta-blockers are not ideal first-line drugs in the treatment of hypertension without compelling indications for their use (such as active CAD and heart failure). Vasodilator beta-blockers (such as carvedilol and nebivolol) may produce better outcomes than traditional beta-blockers; however, this possibility remains speculative.

Theoretically, restoration of nocturnal dipping by dosing some antihypertensive medications at the end of the day seems desirable. However, the impact that nocturnal dosing of antihypertensive medications has on hypertension control and clinical outcomes remains unresolved. The HYGIA study reported significant benefits of evening compared to morning dosing. However, because of the risk of ischemic events from profound nocturnal hypotension and because clinical benefits remain uncertain, many experts have criticized this study and urged caution before general acceptance of nocturnal dosing.

Medications that interrupt the renin-angiotensin cascade are more effective in young, White persons, in whom renin tends to be higher. Calcium channel blockers and diuretics are more effective in older or Black persons, in whom renin levels are generally lower. Many patients require two or more medications and even then a substantial proportion fail to achieve the goal blood pressure. A stepped care approach to the drug treatment of hypertension is outlined in Table 11–11. In diabetic patients, three or four drugs are usually required to reduce systolic blood pressure to goal. In many patients, blood pressure cannot be adequately controlled with any combination. As a result, debating the appropriate first-line agent is less relevant than determining the most appropriate combinations of agents.

Table 11–11. A stepped care approach to the initiation and titration of antihypertension medications.[1,2]

Step 1	ACE inhibitor/ARB **or**[3] Calcium channel blocker **or** Thiazide diuretic[4]
Step 2	ACE inhibitor/ARB **plus** Calcium channel blocker **or** thiazide diuretic[5]
Step 3	ACE inhibitor/ARB **plus** calcium channel blocker **plus** thiazide diuretic
Step 4	ACE inhibitor/ARB **plus** calcium channel blocker **plus** thiazide diuretic **plus** spironolactone[6]

[1]Allow 2 weeks to reach full effect of each drug. Proceed through steps until target blood pressure is attained.
[2]Beta-blockers can be used at any stage if specifically indicated, eg, heart failure or angina.
[3]Initiation with combination therapy should be considered in patients with higher levels of blood pressure and higher cardiovascular risk.
[4]Thiazide or calcium channel blocker is more effective initial therapy in older people and Blacks.
[5]If required, add a calcium channel blocker rather than diuretic in younger patients to avoid long-term exposure to metabolic side effects of diuretics.
[6]Alternatives to spironolactone include eplerenone, amiloride, or triamterene. Watch for hyperkalemia, especially if also receiving ACE inhibitor/ARB. Avoid potassium-sparing diuretics in advanced CKD. If more than three drugs are required at maximum dose, consider specialist referral.

The mnemonic ABCD can be used to remember four classes of antihypertensive medications. These four classes can be divided into two categories: AB and CD. AB refers to drugs that block the RAAS (**A**CE/ARB and **b**eta-blockers). CD refers to those that work in other pathways (**c**alcium channel blockers and **d**iuretics). Combinations of drugs between the two categories are more potent than combinations from within a category. Many experts recommend the use of fixed-dose combination (between two categories) antihypertensive agents as first-line therapy in patients with substantially elevated systolic pressures (greater than 160/100 mm Hg) or difficult-to-control hypertension (which is often associated with diabetes or kidney dysfunction). Because of the unwanted metabolic effects of thiazides, calcium channel blockers may be the preferred second agent in the younger hypertensive patient who is already taking an ACE inhibitor or ARB. However, studies have repeatedly confirmed the effectiveness of thiazide diuretics as first-line agents in prevention of multiple clinical endpoints. Based on the results from the ACCOMPLISH trial, a combination of ACE inhibitor and calcium channel blocker may prove optimal for patients at high risk for cardiovascular events. The initial use of low-dose combinations allows faster blood pressure reduction without substantially higher intolerance rates and is likely to be better accepted by patients. Data from the ALTITUDE study (in patients with type 2 diabetes and CKD or cardiovascular disease or both) indicate that the addition of aliskiren to either ARB or ACE inhibitor was associated with worse outcomes and cannot be recommended, at least in this population. A suggested approach to treatment, tailored to patient demographics, is outlined in Table 11–12.

In sum, as a prelude to treatment, the patient should be informed of common side effects and the need for diligent compliance. In patients with blood pressure less than 160/90 mm Hg in whom pharmacotherapy is indicated, treatment should start with a single agent or two-drug combination at a low dose. Follow-up visits usually should be at 4- to 6-week intervals to allow for full medication effects to be established (especially with diuretics) before further titration or adjustment. If, after titration to usual doses, the patient has shown a discernible but incomplete response and a good tolerance of the initial drug, another medication should be added. See Goals of Treatment, above. As a rule of thumb, a blood pressure reduction of 10 mm Hg can be expected for each antihypertensive agent added to the regimen and titrated to the optimum dose. In those with more severe hypertension, or with comorbidities (such as diabetes) that are likely to render them resistant to treatment, initiation with combination therapy is advised and more frequent follow-up is indicated. Most guidelines recommend the use of home blood pressure monitors in the diagnosis of hypertension. Digital technology makes it possible to monitor the patient's self-measured response to therapy with direct transmission of blood pressure readings to the clinic. The availability of blood pressure profiles generated from multiple home-gathered data points over continuous intervals allows more precise control of the overall hypertensive burden.

Patients who are compliant with their medications and who do not respond to conventional combination regimens should usually be evaluated for secondary hypertension before proceeding to more complex regimens.

Medication Nonadherence

Adherence to antihypertensive treatment is alarmingly poor. In one European study of antihypertensive medication compliance, there was a 40% discontinuation rate at 1 year after initiation. Collaborative care, using clinicians, pharmacists, social workers, and nurses to encourage compliance, has had a variable and often rather modest effect on blood pressure control. Adherence is enhanced by patient education and by use of home blood pressure measurement. The choice of antihypertensive medication is important. Better compliance has been reported for patients whose medications could be taken once daily or as combination pills. Adherence is best with ACE inhibitors and ARBs, and worse with beta-blockers and diuretics.

Table 11–12. Choice of antihypertensive agent based on demographic considerations.[1,2]

	Black Persons, All Ages[3]	All Others, Age < 55 Years	All Others, Age > 55 Years
First-line	CCB or diuretic[4, 5]	ACE inhibitor or ARB[6] or CCB or diuretic[4, 5]	CCB or diuretic[4, 5]
Second-line	ARB[6] or ACE inhibitor[6, 7] or vasodilating beta-blocker[8]	Vasodilating beta-blocker[8]	ACE inhibitor[6] or ARB[6] or vasodilating beta-blocker[8]
Resistant hypertension	Aldosterone receptor blocker	Aldosterone receptor blocker	Aldosterone receptor blocker
Additional options	Centrally acting alpha-agonist or peripheral alpha-antagonist[9]	Centrally acting alpha-agonist or peripheral alpha-antagonist[9]	Centrally acting alpha-agonist or peripheral alpha-antagonist[9]

[1]Compelling indications may alter the selection of an antihypertensive drug.
[2]Start with full dose of one agent, or lower doses of combination therapy. In more severe hypertension (≥ 140/90 mm Hg), consider initiating therapy with a fixed-dose combination.
[3]The reasons why the responses to some medications tend to differ in Black patients are complex and poorly understood. Observations such as these should not be taken as evidence of biological differences based on racial categories.
[4]For patients with significant kidney dysfunction, use loop diuretic instead of thiazide.
[5]The adverse metabolic effects of thiazide diuretics and beta-blockers should be considered in younger patients but may be less important in the older patient.
[6]Women of childbearing age should avoid ACE inhibitors and ARBs or discontinue as soon as pregnancy is diagnosed.
[7]Despite the elevated risk of angioedema and cough in Black patients, ACE inhibitors are generally well tolerated and are a useful adjunct.
[8]There are theoretical advantages in the use of vasodilating beta-blockers such as carvedilol and nebivolol.
[9]Alpha-antagonists may precipitate or exacerbate orthostatic hypotension in older adults.
CCB, calcium channel blocker.

Sex-Specific Considerations in Hypertension

Because of the preponderance of male recruitment into large-scale clinical trials, the impact of a patient's sex on the evaluation and management of hypertension remains uncertain. The limited data that exist suggest a steeper relationship in women between 24-hour ambulatory and nighttime systolic blood pressure and the risk of cardiovascular events. There are many sex-specific effects on the mechanisms and end-organ impact of hypertension. In younger adults, men are more likely to be hypertensive than women, a relationship that reverses in later life. Regression of LVH in response to ACE inhibitors is less pronounced in women. Women are more likely to have isolated systolic hypertension, probably because they develop more active LV systolic function and greater vascular stiffness than men. Fibromuscular dysplasia of the renal artery is much more common in women than men. The side effects of many antihypertensive drugs are more pronounced in women than men, including ACE inhibitor–associated cough and hyponatremia and hypokalemia in response to diuretics. Conversely, thiazides can help preserve bone density. Dependent edema due to amlodipine is more likely in women, and women are more sensitive to beta-blockers. There are no data to support a different blood pressure target in women, but this question has not been examined in dedicated clinical trials.

Treatment of Hypertension in Diabetes

Hypertensive patients with diabetes are at particularly high risk for cardiovascular events. Data from the ACCORD study of diabetic patients demonstrated that most of the benefits of blood pressure lowering were seen with a systolic target of less than 140 mm Hg. Although there was a reduction in stroke risk at a systolic target below 120/70 mm Hg, treatment to this lower target was associated with an *increased* risk of serious adverse effects. US and Canadian guidelines recommend a blood pressure goal of less than 130/80 mm Hg in diabetic patients. Because of the beneficial effects of ACE inhibitors in diabetic nephropathy, they should be part of the initial treatment regimen. ARBs or perhaps renin inhibitors may be substituted in those intolerant of ACE inhibitors. While the ONTARGET study showed that combinations of ACE inhibitors and ARBs in persons with atherosclerosis or type 2 diabetes with end-organ damage appeared to minimize proteinuria, this strategy slightly increased the risks of progression to dialysis and of death; thus, it is not recommended. Most diabetic patients require combinations of three to five agents to achieve target blood pressure, usually including a diuretic and a calcium channel blocker or beta-blocker. Canagliflozin improves glycemic control through inhibition of the sodium-glucose co-transporter 2 (SGLT2) and, in addition, generally lowers blood pressure by 3–4 mm Hg. This drug was associated with improved renal outcomes and reduced cardiovascular risk in the CREDENCE trial of patients with diabetic nephropathy and can be considered when additional blood pressure control is needed in patients with type 2 diabetes. In addition to rigorous blood pressure control, treatment of persons with diabetes should include aggressive treatment of other risk factors.

Treatment of Hypertension in Chronic Kidney Disease

Hypertension is present in 40% of patients with a GFR of 60–90 mL/minute/1.73 m^2 and 75% of patients with a GFR

less than 30 mL/minute/1.73 m^2. The rate of progression of CKD is markedly slowed by treatment of hypertension. In the SPRINT trial, the reduction in cardiovascular risk associated with lower blood pressure targets was also observed in the subgroup with a GFR of less than 60 mL/minute/1.73 m^2. However, an effect of *lower* blood pressure targets on the slowing of CKD progression appears to be restricted to those with pronounced proteinuria. In the SPRINT trial, the lower blood pressure goal was associated with increased risk of AKI, but this was generally reversible and not associated with elevated biomarkers for ischemic injury. Most experts recommend a blood pressure target of less than 130/80 mm Hg in patients with CKD, with consideration of more intensive lowering if proteinuria greater than 1 g per 24 hours is present. Medications that interrupt the renin-angiotensin cascade can slow the progression of kidney disease and are preferred for initial therapy, especially in those with albuminuria of greater than 300 mg/g creatinine. Transition from thiazide to loop diuretic is often necessary to control volume expansion as the eGFR falls below 30 mL/minute/1.73 m^2. ACE inhibitors remain protective and safe in kidney disease associated with significant proteinuria and serum creatinine as high as 5 mg/dL (380 mcmol/L). However, the use of drugs blocking the RAAS cascade in patients with advanced CKD should be supervised by a nephrologist. Kidney function and electrolytes should be measured 1 week after initiating treatment and subsequently monitored carefully in patients with kidney disease. An increase in creatinine of 20–30% is acceptable and expected; more exaggerated responses suggest the possibility of renal artery stenosis or volume contraction. Although lower blood pressure levels are associated with acute decreases in GFR, this appears not to translate into an increased risk of developing ESKD in the long term. Persistence with ACE inhibitor or ARB therapy as the serum potassium level exceeds 5.5 mEq/L is probably not warranted, since other antihypertensive medications are renoprotective as long as goal blood pressures are maintained. However, diuretics can often be helpful in controlling mild hyperkalemia, and there are novel cation exchange polymers (such as patiromer) that sequester potassium in the gut and are more effective and better tolerated than sodium polystyrene sulfonate.

Treatment of Hypertension in Black Patients

Substantial evidence indicates that African Americans are not only more likely to become hypertensive and more susceptible to the cardiovascular and renal complications of hypertension but also respond differently to many antihypertensive medications. The REGARDS study illustrates these differences. At systolic blood pressures less than 120 mm Hg, Black and White Americans between 45 and 64 years of age had equal risk of stroke. For a 10 mm Hg increase in systolic blood pressure, the risk of stroke was threefold higher in Black participants. At levels above 140–159/90–99 mm Hg, the hazard ratio for stroke in Black compared to White participants between 45 and 64 years of age was 2.35. This increased susceptibility may reflect environmental factors, such as structural racism, diet, activity, stress, or access to health care services; differences in occurrence of comorbid conditions such as diabetes or obesity; or genetic ancestry and epigenetics. More studies are needed to determine the source of these differences, and it should be noted that racial disparities are not synonymous with inherent biologic differences based on race. In all persons with hypertension, a multifaceted program of education and lifestyle modification is warranted. Early introduction of combination therapy has been advocated, but there are no clinical trial data to support a lower than usual blood pressure goal in Black patients. Because it appears that ACE inhibitors and ARBs—in the absence of concomitant diuretics—are less effective in Black than in White patients, initial therapy should generally be a diuretic or a diuretic in combination with a calcium channel blocker. However, inhibitors of the RAAS do lower blood pressure in Black patients, are useful adjuncts to the recommended diuretic and calcium channel blockers and should be used in patients with hypertension and compelling indications such as heart failure and kidney disease (especially in the presence of proteinuria) (Table 11–13). *Black patients have an elevated risk of ACE inhibitor–associated angioedema and cough, so ARBs would be the preferred choice.*

Treating Hypertension in Older Adults

Several studies in persons over 60 years of age have confirmed that antihypertensive therapy prevents fatal and

Table 11–13. Recommended antihypertensive medications for coexisting indications.

Indication	Antihypertensive Medication					
	Diuretic	Beta-Blocker	ACE Inhibitor	ARB	Calcium Channel Blocker	Aldosterone Antagonist
Heart failure	√	√	√	√		√
Following MI		√	√			√
High coronary disease risk	√	√	√		√	
Diabetes	√	√	√	√	√	
Chronic kidney disease			√	√		
Recurrent stroke prevention	√		√			

nonfatal MI and reduces overall cardiovascular mortality. The HYVET study indicated that a reasonable ultimate blood pressure goal is 150/80 mm Hg. Updated guidelines suggest that blood pressure goals should not generally be influenced by age alone. An exploratory subgroup analysis of the SPRINT study found that people older than age 75 years showed benefit at the 120 mm Hg systolic treatment target. Importantly, these benefits were also evident in patients classified as frail. This more aggressive approach was, however, associated with greater risk of falls and worsening kidney function, indicating that close monitoring is required in elderly patients treated to lower blood pressure goals. It is also important to note the exclusion criteria of the SPRINT study, which included diabetes mellitus, stroke, and orthostatic hypotension.

Blood pressure treatment goals should be individualized in the very elderly. In the SPRINT MIND study, the lower systolic blood pressure target of 120 mm Hg was associated with a 15% reduction in the incidence of mild cognitive impairment and probable all cause dementia compared to the 140 mm Hg in the target group. Based upon this data, aggressive control of hypertension in high-risk individuals would have a significant impact on the prevalence of dementia. As discussed above, it is important to note that blood pressure measurements in the SPRINT study were made by automated devices, which are known to read lower than conventional office measurements.

How to initiate antihypertensive therapy in older patients—The same medications are used in older patients but at 50% lower doses. Pressure should be reduced more gradually with a safe intermediate systolic blood pressure goal of 160 mm Hg. As treatment is initiated, older patients should be carefully monitored for orthostasis, altered cognition, and electrolyte disturbances. The elderly are especially susceptible to problems associated with polypharmacy, including drug interactions and dosing errors.

Management of Supine Hypertension in Patients With Orthostatic Hypotension

Supine hypertension is common in patients with orthostatic hypotension and is associated with increased cardiovascular risk. Treatment of orthostasis can exacerbate supine hypertension and vice versa. Life expectancy is often reduced in patients with profound autonomic nervous system dysfunction. Treatment of nocturnal hypertension might be considered with the use of shorter acting agents (eg, captopril, hydralazine, losartan, or quick-release nifedipine). In patients with supine hypertension, medications used to increase blood pressure during the day should not be given within 5 hours of bedtime.

Follow-Up of Patients Receiving Hypertension Therapy

Once blood pressure is controlled on a well-tolerated regimen, follow-up visits can be infrequent and laboratory testing limited to those appropriate for the patient and the medications used. Yearly monitoring of blood lipids is recommended, and an ECG could be repeated at 2- to 4-year intervals depending on whether initial abnormalities are present and on the presence of coronary risk factors. Patients who have had excellent blood pressure control for several years, especially if they have lost weight and initiated favorable lifestyle modifications, might be considered for a trial of reduced antihypertensive medications.

Deere BP et al. Hypertension and race/ethnicity. Curr Opin Cardiol. 2020;35:342. [PMID: 32398604]
Milani RV et al. New aspects in the management of hypertension in the digital era. Curr Opin Cardiol. 2021;36:398. [PMID: 33871402]
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Supiano MA et al. New guidelines and SPRINT results: implications for geriatric hypertension. Circulation. 2019;140:976. [PMID: 31525101]
Vogel B et al. The Lancet Women and Cardiovascular Disease Commission: reducing the global burden by 2030. Lancet. 2021;397:2385. [PMID: 34010613]

RESISTANT HYPERTENSION

Resistant hypertension is defined as the failure to reach blood pressure control in patients who are adherent to full doses of an appropriate three-drug regimen (including a diuretic). In the approach to resistant hypertension, the clinician should first confirm compliance and rule out "white coat hypertension," ideally using ambulatory or home-based measurement of blood pressure. Exacerbating factors should be considered (as outlined above). Finally, identifiable causes of resistant hypertension should be sought (Table 11–14). The clinician should pay particular attention to the type of diuretic being used in relation to the patient's kidney function. Aldosterone may play an important role in resistant hypertension and aldosterone receptor blockers can be very useful. If goal blood pressure cannot be achieved following completion of these steps, consultation with a hypertension specialist should be considered. Renal sympathetic nerve ablation is a consideration for these patients in the absence of other options, but further trials are needed before this procedure can be routinely integrated into clinical practice.

Wei FF et al. Diagnosis and management of resistant hypertension: state of the art. Nat Rev Nephrol. 2018;14:428. [PMID: 29700488]

HYPERTENSIVE URGENCIES & EMERGENCIES

Hypertensive urgencies are situations in which blood pressure must be reduced within a few hours. These include patients with asymptomatic severe hypertension (systolic blood pressure greater than 220 mm Hg or diastolic pressure greater than 125 mm Hg that persists after a period of observation) and those with optic disk edema, progressive target-organ complications, and severe perioperative hypertension. Elevated blood pressure levels alone—in the absence of symptoms of new or progressive

Table 11–14. Causes of resistant hypertension.

Improper blood pressure measurement
Nonadherence
Volume overload and pseudotolerance
Excess sodium intake
Volume retention from kidney disease
Inadequate diuretic therapy
Drug-induced or other causes
Inadequate doses
Inappropriate combinations
NSAIDs; cyclooxygenase-2 inhibitors
Cocaine, amphetamines, other illicit drugs
Sympathomimetics (decongestants, anorectics)
Oral contraceptives
Adrenal steroids
Cyclosporine and tacrolimus
Erythropoietin
Licorice (including some chewing tobacco)
Selected over-the-counter dietary supplements and medicines (eg, ephedra, ma huang, bitter orange)
Associated conditions
Obesity
Excess alcohol intake
Identifiable causes of hypertension (see Table 11–2)

Data from Chobanian AV et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289:2560.

target-organ damage—rarely require emergency therapy. Parenteral drug therapy is not usually required; partial reduction of blood pressure with relief of symptoms is the goal. Effective oral agents are clonidine, captopril, and slow-release nifedipine.

Hypertensive emergencies require substantial reduction of blood pressure within 1 hour to avoid the risk of serious morbidity or death. Although blood pressure is usually strikingly elevated (diastolic pressure greater than 130 mm Hg), the correlation between pressure and end-organ damage is often poor. *It is the presence of critical multiple end-organ injury that determines the seriousness of the emergency and the approach to treatment.* Emergencies include hypertensive encephalopathy (headache, irritability, confusion, and altered mental status due to cerebrovascular spasm), hypertensive nephropathy (hematuria, proteinuria, and AKI due to arteriolar necrosis and intimal hyperplasia of the interlobular arteries), intracranial hemorrhage, aortic dissection, preeclampsia-eclampsia, pulmonary edema, unstable angina, or myocardial infarction. Encephalopathy or nephropathy accompanying hypertensive retinopathy has historically been called malignant hypertension, but the therapeutic approach is identical to that used in other hypertensive emergencies.

Parenteral therapy is indicated in most hypertensive emergencies, especially if encephalopathy is present. The initial goal in hypertensive emergencies is to reduce the pressure by no more than 25% (within minutes to 1 or 2 hours) and then toward a level of 160/100 mm Hg within 2–6 hours. Excessive reductions in pressure may precipitate coronary, cerebral, or renal ischemia. To avoid such declines, the use of agents that have a predictable, dose-dependent, transient, and progressive antihypertensive effect is preferable (Table 11–15). *In that regard, the use of sublingual or oral fast-acting nifedipine preparations is best avoided.*

Acute ischemic stroke is often associated with marked elevation of blood pressure, which will usually fall spontaneously. In such cases, antihypertensives should only be used if the systolic blood pressure exceeds 180–200 mm Hg, and blood pressure should be reduced cautiously by 10–15% over 24 hours (Table 11–15). If thrombolytics are to be given, blood pressure should be maintained at less than 185/110 mm Hg during treatment and for 24 hours following treatment.

In **intracerebral hemorrhage,** the aim is to minimize bleeding by reducing the systolic blood pressure in most patients to 140 mm Hg within the first 6 hours. In acute subarachnoid hemorrhage, as long as the bleeding source remains uncorrected, a compromise must be struck between preventing further bleeding and maintaining cerebral perfusion in the face of cerebral vasospasm. In this situation, blood pressure goals depend on the patient's usual blood pressure. In previously normotensive patients, the target should be a systolic blood pressure of 110–120 mm Hg; in hypertensive patients, blood pressure should be reduced to 20% below baseline pressure. In the treatment of hypertensive emergencies complicated by (or precipitated by) CNS injury, labetalol and nicardipine are good choices since they are nonsedating and do not appear to cause significant increases in cerebral blood flow or intracranial pressure. Patients with subarachnoid hemorrhage should receive nimodipine for 3 weeks following presentation to minimize cerebral vasospasm. *In hypertensive emergencies arising from catecholaminergic mechanisms, such as pheochromocytoma or cocaine use, beta-blockers can worsen the hypertension because of unopposed peripheral vasoconstriction; nicardipine, clevidipine, or phentolamine is preferred.* Labetalol is useful in these patients if the heart rate must be controlled but should not be used as first-line therapy because it exhibits more beta- than alpha-blockade. Table 11–15 provides guidelines for the choice of antihypertensive agent based on the site of end-organ damage. ACE inhibitors are specifically indicated for hypertensive crisis from systemic sclerosis (scleroderma).

In acute aortic dissection, systolic blood pressure and heart rate should be reduced within 30 minutes to below 120 mm Hg and less than 60 beats per minute, using a combination of vasodilation and beta-blockade.

Pharmacologic Management

A. Parenteral Agents

Sodium nitroprusside is no longer the treatment of choice for acute hypertensive problems; in most situations, appropriate control of blood pressure is best achieved using combinations of nicardipine or clevidipine plus labetalol or esmolol. (Table 11–16 lists drugs, dosages, and adverse effects.)

1. Nicardipine—Intravenous nicardipine is the most potent and the longest acting of the parenteral calcium channel blockers. As a primarily arterial vasodilator, it has

Table 11–15. Treatment of hypertensive emergency depending on primary site of end-organ damage. *See* Table 11–16 *for dosages.*

Type of Hypertensive Emergency	Recommended Drug Options and Combinations	Drugs to Avoid
Myocardial ischemia and infarction	Nicardipine plus esmolol[1] Nitroglycerin plus labetalol Nitroglycerin plus esmolol[1]	Hydralazine, diazoxide, minoxidil, nitroprusside
Acute kidney injury	Fenoldopam Nicardipine Clevidipine	
Aortic dissection	Esmolol plus nicardipine Esmolol plus clevidipine Labetalol Esmolol plus nitroprusside	Hydralazine, diazoxide, minoxidil
Acute pulmonary edema, LV systolic dysfunction	Nicardipine plus nitroglycerin[2] plus a loop diuretic Clevidipine plus nitroglycerin[2] plus a loop diuretic	Hydralazine, diazoxide, beta-blockers
Acute pulmonary edema, diastolic dysfunction	Esmolol plus low-dose nitroglycerin plus a loop diuretic Labetalol plus low-dose nitroglycerin plus a loop diuretic	
Ischemic stroke (systolic blood pressure > 180–200 mm Hg)	Nicardipine Clevidipine Labetalol	Nitroprusside, methyldopa, clonidine, nitroglycerin
Intracerebral hemorrhage (systolic blood pressure > 140–160 mm Hg)	Nicardipine Clevidipine Labetalol	Nitroprusside, methyldopa, clonidine, nitroglycerin
Hyperadrenergic states, including cocaine use	Nicardipine plus a benzodiazepine Clevidipine plus a benzodiazepine Phentolamine Labetalol	Beta-blockers
Preeclampsia, eclampsia	Labetalol Nicardipine	Diuretics, ACE inhibitors

[1]Avoid if there is LV systolic dysfunction.
[2]Drug of choice if LV systolic dysfunction is associated with ischemia.

the potential to precipitate reflex tachycardia, and for that reason, it should not be used without a beta-blocker in patients with CAD.

2. Clevidipine—Intravenous clevidipine is an L-type calcium channel blocker with a 1-minute half-life, which facilitates swift and tight control of severe hypertension. It acts on arterial resistance vessels and is devoid of venodilatory or cardiodepressant effects.

3. Labetalol—This combined beta- and alpha-blocking agent is the most potent adrenergic blocker for rapid blood pressure reduction. Other beta-blockers are far less potent. Excessive blood pressure drops are unusual. Experience with this agent in hypertensive syndromes associated with pregnancy has been favorable.

4. Esmolol—This rapidly acting beta-blocker is approved only for treatment of supraventricular tachycardia, but is often used for lowering blood pressure. It is less potent than labetalol and should be reserved for patients in whom there is particular concern about serious adverse events related to beta-blockers.

5. Fenoldopam—Fenoldopam is a peripheral dopamine-1 (DA_1) receptor agonist that causes a dose-dependent reduction in arterial pressure without evidence of tolerance, rebound, withdrawal, or deterioration of kidney function. In higher dosage ranges, tachycardia may occur. This drug is natriuretic, which may simplify volume management in AKI.

6. Enalaprilat—This is the active form of the oral ACE inhibitor enalapril. The onset of action is usually within 15 minutes, but the peak effect may be delayed for up to 6 hours. Thus, enalaprilat is used primarily as an adjunctive agent.

7. Diuretics—Intravenous loop diuretics can be very helpful when the patient has signs of heart failure or fluid retention, but the onset of their hypotensive response is slow, making them an adjunct rather than a primary agent for hypertensive emergencies. Low dosages should be used initially (furosemide, 20 mg, or bumetanide, 0.5 mg). They facilitate the response to vasodilators, which often stimulate fluid retention.

8. Hydralazine—Hydralazine can be given intravenously or intramuscularly, but its effect is less predictable than that of other drugs in this group. It produces reflex tachycardia and should not be given without beta-blockers in patients

Table 11–16. Drugs for hypertensive emergencies and urgencies (in descending order of preference).

Agent	Action	Dosage	Onset	Duration	Adverse Effects	Comments
Hypertensive Emergencies						
Nicardipine (Cardene)	Calcium channel blocker	5 mg/hour intravenously; may increase by 1–2.5 mg/hour every 15 minutes to 15 mg/hour	1–5 minutes	3–6 hours	Hypotension, tachycardia, headache.	May precipitate myocardial ischemia.
Clevidipine (Cleviprex)	Calcium channel blocker	1–2 mg/hour intravenously initially; double rate every 90 seconds until near goal, then by smaller amounts every 5–10 minutes to a maximum of 32 mg/hour	2–4 minutes	5–15 minutes	Headache, nausea, vomiting.	Lipid emulsion: contraindicated in patients with allergy to soy or egg.
Labetalol (Trandate)	Beta- and alpha-blocker	20–40 mg intravenously every 10 minutes to 300 mg; 2 mg/minute infusion	5–10 minutes	3–6 hours	Nausea, hypotension, bronchospasm, bradycardia, heart block.	Avoid in acute LV systolic dysfunction, asthma. May be continued orally.
Esmolol (Brevibloc)	Beta-blocker	Loading dose 500 mcg/kg intravenously over 1 minute; maintenance, 25–200 mcg/kg/minute	1–2 minutes	10–30 minutes	Bradycardia, nausea.	Avoid in acute LV systolic dysfunction, asthma. Weak antihypertensive.
Fenoldopam (Corlopam)	Dopamine receptor agonist	0.1–1.6 mcg/kg/minute intravenously	4–5 minutes	< 10 minutes	Reflex tachycardia, hypotension, increased intraocular pressure.	May protect kidney function.
Enalaprilat (Vasotec)	ACE inhibitor	1.25 mg intravenously every 6 hours	15 minutes	6 hours or more	Excessive hypotension.	Additive with diuretics; may be continued orally.
Furosemide (Lasix)	Diuretic	10–80 mg orally or intravenously	15 minutes	4 hours	Hypokalemia, hypotension.	Adjunct to vasodilator.
Hydralazine (Apresoline)	Vasodilator	5–20 mg intravenously; may repeat after 20 minutes	10–30 minutes	2–6 hours	Tachycardia, headache, vomiting, diarrhea	Avoid in CAD, dissection. Rarely used except in pregnancy.
Nitroglycerin	Vasodilator	0.25–5 mcg/kg/minute intravenously	2–5 minutes	3–5 minutes	Headache, nausea, hypotension, bradycardia.	Tolerance may develop. Useful primarily with myocardial ischemia.
Nitroprusside (Nitropress)	Vasodilator	0.25–10 mcg/kg/minute intravenously	Seconds	3–5 minutes	Anxiety, increased intracranial pressure, vomiting, bowel obstruction; thiocyanate and cyanide toxicity, especially with kidney and liver dysfunction; hypotension. Coronary steal, decreased cerebral blood flow, increased intracranial pressure.	No longer the first-line agent.
Hypertensive Urgencies						
Clonidine (Catapres)	Central sympatholytic	0.1–0.2 mg orally initially; then 0.1 mg every hour to 0.8 mg orally	30–60 minutes	6–8 hours	Sedation.	Rebound may occur.
Captopril (Capoten)	ACE inhibitor	12.5–25 mg orally	15–30 minutes	4–6 hours	Excessive hypotension.	
Nifedipine (Adalat, Procardia)	Calcium channel blocker	10 mg orally initially; may be repeated after 30 minutes	15 minutes	2–6 hours	Excessive hypotension, tachycardia, headache, angina, myocardial infarction, stroke.	Response unpredictable.

with possible coronary disease or aortic dissection. Hydralazine is used primarily in pregnancy and in children, but even in these situations, it is not a first-line drug.

9. Nitroglycerin, intravenous—This agent should be reserved for patients with accompanying acute coronary ischemic syndromes.

10. Nitroprusside sodium—This agent is given by controlled intravenous infusion gradually titrated to the desired effect. It lowers the blood pressure within seconds by direct arteriolar and venous dilation. Monitoring with an intra-arterial line avoids hypotension. Nitroprusside—in combination with a beta-blocker—is useful in patients with aortic dissection.

B. Oral Agents

Patients with less severe acute hypertensive syndromes can often be treated with oral therapy. Suitable drugs will reduce the blood pressure over a period of hours. In those presenting as a consequence of noncompliance, it is usually sufficient to restore the patient's previously established oral regimen.

1. Clonidine—Clonidine, 0.2 mg orally initially, followed by 0.1 mg every hour to a total of 0.8 mg, will usually lower blood pressure over a period of several hours. Sedation is frequent, and rebound hypertension may occur if the drug is stopped.

2. Captopril—Captopril, 12.5–25 mg orally, will also lower blood pressure in 15–30 minutes. The response is variable and may be excessive. Captopril is the drug of choice in the management of systemic sclerosis hypertensive crisis.

3. Nifedipine—The effect of fast-acting nifedipine capsules is unpredictable and may be excessive, resulting in hypotension and reflex tachycardia. Because MI and stroke have been reported in this setting, the use of sublingual nifedipine is not advised. Nifedipine retard, 20 mg orally, appears to be safe and effective.

C. Subsequent Therapy

When the blood pressure has been brought under control, combinations of oral antihypertensive agents can be added as parenteral drugs are tapered off over a period of 2–3 days.

Jolly H et al. Management of hypertensive emergencies and urgencies: narrative review. Postgrad Med J. 2021 Oct 20. [Epub ahead of print] [PMID: 34670853]

Blood Vessel & Lymphatic Disorders

12

Warren J. Gasper, MD
James C. Iannuzzi, MD, MPH
Meshell D. Johnson, MD

ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

Occlusive atherosclerotic lesions in the extremities, or peripheral artery disease (PAD), is evidence of a systemic atherosclerotic process. The prevalence of PAD is 30% in patients who are 70 years old without other risk factors, or 50 years old with risk factors such as diabetes mellitus or tobacco use. Pathologic changes of atherosclerosis may be diffuse, but flow-limiting stenoses occur segmentally. In the lower extremities, stenoses classically occur in three anatomic segments: the aortoiliac segment, femoral-popliteal segment, and the infrapopliteal or tibial segment of the arterial tree.

Approximately two-thirds of patients with PAD are either asymptomatic or do not have classic symptoms. Intermittent claudication, which is pain with ambulation that occurs from insufficient blood flow relative to demand, is typically described as severe and cramping primarily in the calf muscles.

OCCLUSIVE DISEASE: AORTA & ILIAC ARTERIES

ESSENTIALS OF DIAGNOSIS

- Claudication: cramping pain or tiredness in the calf, thigh, or hip while walking.
- Diminished femoral pulses.
- Tissue loss (ulceration, gangrene) or rest pain.

General Considerations

Lesions in the distal aorta and proximal common iliac arteries classically occur in White men aged 50–60 years who smoke cigarettes. Disease progression may lead to complete occlusion of one or both common iliac arteries, which can precipitate occlusion of the entire abdominal aorta to the level of the renal arteries.

Clinical Findings

A. Symptoms and Signs

The pain from aortoiliac lesions may extend into the thigh and buttocks and erectile dysfunction may occur from bilateral common iliac disease. Rarely, patients complain only of weakness in the legs when walking, or simply extreme limb fatigue. The symptoms are relieved with rest and are reproducible when the patient walks again. Femoral pulses and distal pulses are absent or very weak. Bruits may be heard over the aorta, iliac, and femoral arteries.

B. Doppler and Vascular Findings

The ratio of systolic blood pressure detected by Doppler examination at the ankle compared with the brachial artery (referred to as the ankle-brachial index [ABI]) is reduced to below 0.9 (normal ratio is 0.9–1.2); this difference is exaggerated by exercise. Both the dorsalis pedis and the posterior tibial arteries are measured and the higher of the two artery pressures is used for calculation. Segmental waveforms or pulse volume recordings obtained by strain gauge technology through blood pressure cuffs demonstrate blunting of the arterial inflow throughout the lower extremity.

C. Imaging

CT angiography (CTA) and magnetic resonance angiography (MRA) can identify the anatomic location of disease. Due to overlying bowel, duplex ultrasound has a limited role in imaging the aortoiliac segment. Imaging is required only when symptoms necessitate intervention, since a history and physical examination with vascular testing should appropriately identify the involved levels of the arterial tree.

Treatment

A. Medical and Exercise Therapy

The cornerstones of aortoiliac disease treatment are cardiovascular risk factor reduction and a supervised or structured exercise program. Essential elements include cigarette smoking cessation, antiplatelet therapy, lipid and blood

pressure management, and weight loss. Nicotine replacement therapy, bupropion, and varenicline have established benefits in cigarette smoking cessation (see Chapter 1). While no longer recommended for primary prevention of CVD, antiplatelet agents (aspirin [81 mg orally daily] or clopidogrel [75 mg orally daily]) remain important for secondary prevention of cardiovascular events in those with PAD and to reduce peripheral vascular morbidity. Low-dose rivaroxaban (2.5 mg orally twice daily) with aspirin 100 mg orally daily reduces both major cardiovascular and limb-related adverse events in symptomatic patients. All patients with PAD should receive high-dose statin (eg, atorvastatin 80 mg daily if tolerated) to treat hypercholesterolemia and arterial inflammation. A trial of cilostazol, 100 mg orally twice a day, may improve walking distance in approximately two-thirds of patients but may take 2–4 weeks to be effective and 12 weeks until full effect.

Supervised exercise programs for PAD provide significant improvements in pain, walking distance, and quality of life and may be more effective than an endovascular treatment alone. A minimum training goal is a walking session of 30–45 minutes at least 3 days per week for a minimum of 12 weeks. Structured community or home-based exercise programs as well as alternative exercises (cycling, upper-body ergometry) may also be effective. The Society for Vascular Surgery Supervised Exercise Therapy App, a patient-facing mobile app, has shown promise.

B. Endovascular Therapy

Focal atherosclerotic lesions in the aorta or iliac arteries can be effectively treated with angioplasty and stenting. This approach matches the results of surgery for single stenoses but both effectiveness and durability decrease with longer or multiple stenoses.

C. Surgical Intervention

A prosthetic aorto-femoral bypass graft that bypasses the diseased aorta or iliac artery segments is a highly effective and durable treatment for this disease. Patients may also be treated with a graft from the axillary artery to the femoral arteries (axillo-femoral bypass graft) or with a graft from the contralateral femoral artery (femoral-femoral bypass) when iliac disease is limited to one side. The operative risk of axillo-femoral and femoral-to-femoral bypass grafts is lower because the abdominal cavity is not entered and the aorta is not cross-clamped, but the grafts are less durable.

Complications

The complications of aorto-femoral bypass are those of any major abdominal surgery in a patient population with a high prevalence of CVD. Mortality is low (2–3%), but morbidity is higher and includes a 5–10% rate of MI. While endovascular approaches are safer and the complication rate is 1–3%, they are less durable with extensive disease.

Prognosis

Patients with isolated aortoiliac disease may have a further reduction in walking distance without intervention, but symptoms rarely progress to rest pain or threatened limb loss. Life expectancy is limited by attendant CVD with a mortality rate of 25–40% at 5 years.

Symptomatic relief is generally excellent with supervised exercise or after intervention. After aorto-femoral bypass, a patency rate of 90% at 5 years is reported. Endovascular patency rates and symptom relief for patients with short stenoses are also good with 80% symptom free at 3 years. Recurrence rates following endovascular treatment of extensive disease are 30–50%.

When to Refer

Patients with progressive reduction in walking distance despite risk factor modification and supervised exercise programs and those with limitations that interfere with their activities of daily living should be referred for consultation to a vascular surgeon.

When to Admit

- Patients with evidence of chronic limb-threatening ischemia, including lower extremity rest pain and tissue loss since these may quickly progress to limb-threatening conditions.
- Patients with acute limb ischemia should also be admitted with intravenous anticoagulation and surgical consultation.
- Patients with acute limb ischemia for treatment with intravenous anticoagulation and to obtain surgical consultation.

Bonaca M P et al. Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med. 2020;382:1994. [PMID: 32222135]

Morcos R et al. The evolving treatment of peripheral arterial disease through guideline-directed recommendations. J Clin Med. 2018;7:9. [PMID: 29315259]

OCCLUSIVE DISEASE: FEMORAL & POPLITEAL ARTERIES

ESSENTIALS OF DIAGNOSIS

- Cramping pain or tiredness in the calf with exercise.
- Reduced popliteal and pedal pulses.
- Foot pain at rest, relieved by dependency.
- Foot gangrene or ischemic ulcers.

General Considerations

The superficial femoral artery is the peripheral artery most commonly occluded by atherosclerosis. Atherosclerosis of the femoral-popliteal segment usually occurs about a decade after the development of aortoiliac disease, has an even gender distribution, and commonly affects Black and

Latinx patients. The disease frequently occurs where the superficial femoral artery passes through the abductor magnus tendon in the distal thigh (Hunter canal). The common femoral artery and the popliteal artery are less often diseased but lesions in these vessels are debilitating, resulting in short-distance claudication.

Clinical Findings

A. Symptoms and Signs

Symptoms of intermittent claudication caused by lesions of the common femoral artery, superficial femoral artery, and popliteal artery are confined to the calf. Claudication occurs at 2–4 blocks when there is occlusion or stenosis of the superficial femoral artery at the adductor canal, provided good collateral vessels from the profunda femoris are maintained. However, with concomitant disease of the profunda femoris or the popliteal artery, much shorter distances may trigger symptoms. With short-distance claudication, dependent rubor of the foot may be present; pallor on elevation distinguishes rubor from erythema. Chronic low blood flow states will also cause atrophic changes in the lower leg and foot with loss of hair, thinning of the skin and subcutaneous tissues, and disuse atrophy of the muscles. With segmental occlusive disease of the superficial femoral artery, the common femoral pulsation is normal, but the popliteal and pedal pulses are reduced.

B. Doppler and Vascular Findings

ABI values less than 0.9 are diagnostic of PAD and levels below 0.4 suggest chronic limb-threatening ischemia (formerly critical limb ischemia). ABI readings depend on arterial compression; since vessels may be calcified in diabetes mellitus, CKD, and in older adults, ABIs can be misleading. In such patients, the toe-brachial index is usually reliable with a value less than 0.7 considered diagnostic of PAD. Pulse volume recordings with cuffs placed at the high thigh, mid-thigh, calf, and ankle will delineate the levels of obstruction with reduced pressures and blunted waveforms.

C. Imaging

Duplex ultrasonography, CTA, and MRA all adequately show the anatomic location of the obstructive lesions and are performed only if revascularization is planned. After revascularization, patients can be monitored with annual ultrasonograms.

Treatment

A. Medical and Exercise Therapy

As with aortoiliac disease, risk factor reduction, medical optimization with an antiplatelet agent, high-dose statin, and exercise treatment are the cornerstone of therapy. Dual treatment with rivaroxaban (2.5 mg orally twice daily) and aspirin (81 mg orally daily) has been shown to reduce limb-related events, major amputation, and cardiovascular events. Cilostazol, 100 mg orally twice a day, may improve intermittent claudication symptoms.

B. Surgical Intervention

Intervention is indicated if claudication is progressive, incapacitating, or interferes significantly with essential daily activities or employment. Intervention is mandatory if there is ischemic rest pain or ischemic ulcers threaten the foot.

1. Bypass surgery—The most effective and durable treatment for superficial femoral artery lesions is a femoral-popliteal bypass with autologous saphenous vein. Synthetic material, usually polytetrafluoroethylene, can be used, but these grafts do not have the durability of vein bypass.

2. Endovascular techniques—Endovascular techniques, such as angioplasty and stenting, are often used for lesions of the superficial femoral artery. These techniques have lower morbidity than bypass surgery but also have decreased durability.

Endovascular therapy is most effective in patients undergoing aggressive risk factor modification in whom lesions measure less than 10 cm long. Paclitaxel-eluting stents or paclitaxel-coated balloons offer modest improvement over bare metal stents and noncoated balloons, but the effect is not as robust as in the coronary arteries. The 1-year patency rate is 50% for balloon angioplasty, 70% for drug-coated balloons, 80% for bare metal stents, and 90% for drug-eluting stents. However, by 3 years, the patency rates are significantly worse for all four techniques and reintervention for restenosis is common. After a meta-analysis of clinical trial data showed increased mortality at 3–5 years after treatment with paclitaxel-coated devices, the US FDA recommends judicious use of the devices. However, an interim analysis of the SWEDEPAD trial demonstrated no significant difference in all-cause mortality at 2.5 years; similarly, a subgroup analysis of the VOYAGER PAD trial found no mortality difference between drug-coated devices and angioplasty.

3. Thromboendarterectomy—Removal of the atherosclerotic plaque is limited to the lesions of the common femoral and the profunda femoris arteries where bypass grafts and endovascular techniques have a more limited role.

Complications

Open surgical procedures of the lower extremities, particularly long bypasses with vein harvest, have a risk of wound infection that is higher than in other areas of the body. Wound infection or seroma can occur in as many as 10–15% of cases. MI rates after open surgery are 5–10%, with a 1–4% mortality rate. Complication rates of endovascular surgery are 1–5%, making these therapies attractive despite their lower durability.

Prognosis

The prognosis for motivated patients with isolated superficial femoral artery disease is excellent, and surgery is not recommended for mild or moderate claudication in these patients. However, when claudication significantly limits daily activity and cardiovascular health, intervention may be warranted. All interventions require close postprocedure

follow-up with repeated ultrasound surveillance so that recurrent narrowing can be treated promptly with angioplasty or bypass to prevent complete occlusion. The reported patency rate of bypass grafts of the femoral artery, superficial femoral artery, and popliteal artery is 65–70% at 3 years, whereas the patency of angioplasty is less than 50% at 3 years.

Because of the extensive atherosclerotic disease, including associated coronary lesions, 5-year survival with lower extremity PAD is 70% and decreases to 50% when there is involvement of the tibial arteries. However, with aggressive risk factor modification, substantial improvement in longevity has been reported.

When to Refer

Patients with progressive symptoms, short-distance claudication, rest pain, or any ulceration should be referred to a peripheral vascular specialist.

When to Admit

Individuals presenting with chronic limb threatening ischemia (eg, ischemic rest pain, tissue loss) may warrant admission because of a high risk of progression to limb loss. If there is concern for a foot infection, particularly in patients with diabetes, admission for broad-spectrum antibiotics and emergent surgical evaluation should be considered since emergent debridement may be necessary to prevent ascending infections that could be limb- and life-threatening.

Bauersachs RM et al. Total ischemic event reduction with rivaroxaban after peripheral arterial revascularization in the VOYAGER PAD Trial. J Am Coll Cardiol. 2021;78:317. [PMID: 34010631]

Nordanstig J et al. Mortality with paclitaxel-coated devices in peripheral artery disease. N Engl J Med. 2020;383:2538. [PMID: 33296560]

OCCLUSIVE DISEASE: TIBIAL & PEDAL ARTERIES

ESSENTIALS OF DIAGNOSIS

- Severe pain of the forefoot that is relieved by dependency (ischemic rest pain).
- Pain or numbness of the foot with walking.
- Ulcer or gangrene, and not claudication, is a frequent initial manifestation.
- Pallor when the foot is elevated.

General Considerations

Occlusive processes of the tibial arteries of the lower leg and pedal arteries in the foot occur primarily in patients with diabetes. There often is extensive calcification of the artery wall.

Clinical Findings

A. Symptoms and Signs

Unless there are concomitant lesions in the aortoiliac or femoral/superficial femoral artery segments, the first manifestation of leg ischemia due to tibial artery disease is frequently an ischemic ulcer or foot gangrene, rather than claudication. Chronic limb-threatening ischemia is defined as the presence of ischemic rest pain or ulcers and is associated with the highest rate of amputation. Classically, ischemic rest pain is confined to the dorsum of the foot and is relieved with dependency: the pain does not occur with standing, sitting, or dangling the leg over the edge of the bed. It is severe and burning in character, and because it is present only when recumbent, it may awaken the patient from sleep.

On examination, femoral and popliteal pulses may or may not be present depending on disease extent, but palpable pedal pulses will be absent. Dependent rubor may be prominent with pallor on elevation. The skin of the foot is generally cool, atrophic, and hairless.

B. Doppler and Vascular Findings

The ABI is often below 0.4; however, the ABI may be falsely elevated due to calcification of the arterial media layer (Mönckeberg medial calcific sclerosis) and may not be compressible. Toe-brachial indexes are preferred for assessing perfusion and predicting wound healing.

C. Imaging

Digital subtraction angiography is the gold standard method to delineate the anatomy of the tibial-popliteal segment. MRA or CTA is less helpful for detection of lesions in this location due to the small vasculature and other technical issues related to image resolution.

Differential Diagnosis

It is important to differentiate rest pain from diabetic neuropathic dysesthesia. Leg night cramps cause pain in the leg rather than the foot and should not be confused with ischemic rest pain. Dependent rubor in the presence of a toe wound can often be mistaken for cellulitis; pallor on elevation helps confirm the diagnosis of rubor.

Treatment

Good foot care may prevent ulcers, and most diabetic patients will do well with a conservative regimen. However, if ulcerations appear and there is no significant healing within 2–3 weeks, blood flow studies (ankle-brachial index/toe-brachial index) are indicated. Poor blood flow and a foot ulcer or nightly ischemic rest pain requires expeditious revascularization to avoid a major amputation.

A. Bypass and Endovascular Techniques

Bypass with vein to the distal tibial or pedal arteries is an effective therapy to treat rest pain and heal ischemic foot ulcers. Because the foot often has relative sparing of vascular disease, these bypasses have had adequate patency rates

(70% at 3 years). In nearly all series, limb preservation rates are much higher than patency rates.

Endovascular treatment of tibial or pedal artery disease with plain balloon angioplasty is effective for short segment lesions. The technical failure and reocclusion rates increase drastically with long segment disease in multiple tibial arteries. Stents and drug-coated balloons have not been successful in the tibial vessels to date.

B. Amputation

Patients with ischemic rest pain or ulcers have a 30–40% 1-year risk for major amputation that increases if revascularization cannot be done. Because of the distal nature of the tibial artery disease, diabetic patients are more likely to be asymptomatic until more severe ischemic disease with tissue loss develops, which can be exacerbated by peripheral neuropathy. Diabetic patients with PAD have a 4-fold risk of chronic limb-threatening ischemia compared with nondiabetic patients with PAD and have a risk of amputation up to 20-fold when compared to an age-matched population. Tibial artery disease is a major risk factor for amputation and is included as a factor in the Global Limb Anatomic Staging System (GLASS) vascular guidelines.

Complications

The complications of intervention are similar to those listed for superficial femoral artery disease; the overall cardiovascular risk of intervention increases with decreasing ABI. Patients with chronic limb-threatening ischemia require aggressive risk factor modification. Wound infection rates after bypass are higher if there is an open wound in the foot.

Prognosis

Patients with tibial atherosclerosis have extensive atherosclerotic burden and a high prevalence of diabetes. Their prognosis without intervention is poor and complicated by the risk of amputation.

When to Refer

Patients with diabetes and foot ulcers should be referred for a formal vascular evaluation.

When to Admit

Any diabetic patient with a foot ulcer and foot infection should be evaluated for an emergent operative incision and drainage. Broad-spectrum intravenous antibiotics should be given empirically (eg, vancomycin to cover methicillin-resistant *Staphylococcus aureus* [MRSA] plus either ertapenem or piperacillin/tazobactam to cover gram-negative and anaerobic organisms). Multidisciplinary limb preservation centers, staffed with vascular surgeons, podiatrists, plastic and orthopedic surgeons, prosthetics and orthotic specialists, and diabetes specialists, should be sought since they have improved limb salvage rates.

Conte MS et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg. 2019;69:3. [PMID: 31159978]

ACUTE ARTERIAL OCCLUSION OF A LIMB

ESSENTIALS OF DIAGNOSIS

- Sudden pain in a limb with absent limb pulses.
- Usually some neurologic dysfunction with numbness, weakness, or complete paralysis.
- Loss of light touch sensation requires revascularization within 3 hours for limb viability.

General Considerations

Acute occlusion may be due to an embolus or to thrombosis of a diseased atherosclerotic segment. Emboli large enough to occlude proximal arteries in the lower extremities are almost always cardiac in origin. Atrial fibrillation is the most common cause of cardiac thrombus formation; other causes are valvular disease or thrombus formation on the ventricular surface of a large anterior myocardial infarct.

Emboli from arterial sources such as arterial ulcerations or calcified excrescences are usually small and go to the distal arterial tree (toes).

The typical patient with primary thrombosis will have a history of claudication and an abrupt worsening of symptoms. If the stenosis is chronic, collateral blood vessels will develop, and the resulting occlusion may cause only a minimal increase in symptoms.

Clinical Findings

A. Symptoms and Signs

The sudden onset of extremity pain, with loss or reduction in pulses, is diagnostic of acute arterial occlusion. This often will be accompanied by neurologic dysfunction, such as numbness or paralysis in extreme cases. With popliteal occlusion, symptoms may affect only the foot. With proximal occlusions, the whole leg may be affected. Signs of severe arterial ischemia include pallor, coolness of the extremity, and mottling. Impaired neurologic function progressing to anesthesia with paralysis indicates irreversible injury requiring amputation.

B. Doppler and Laboratory Findings

There will be little or no flow found with Doppler examination of the distal vessels. Imaging, if done, may show an abrupt cutoff of contrast with embolic occlusion. Blood work may show myoglobinemia and metabolic acidosis.

C. Imaging

Whenever possible, imaging should be done in the operating room because obtaining angiography, MRA, or CTA may delay revascularization and jeopardize the viability of the extremity. However, in cases with only modest symptoms and where light touch of the extremity is maintained, imaging may be helpful in planning the revascularization procedure.

Treatment

Immediate revascularization is required in all cases of symptomatic acute arterial thrombosis. *Evidence of neurologic injury, including loss of light touch sensation, indicates that collateral flow is inadequate to maintain limb viability and revascularization should be accomplished within 3 hours.* Longer delays carry a significant risk of irreversible tissue damage approaching 100% at 6 hours.

A. Heparin

As soon as the diagnosis is made, an initial weight-based bolus of unfractionated heparin should be infused intravenously (80 units/kg) followed by a continuous heparin infusion to maintain the activated partial thromboplastin time (aPTT) in the therapeutic range (60–85 seconds) (12–18 units/kg/hour). This helps prevent clot propagation and may also relieve associated vessel spasm. Anticoagulation may improve symptoms, but revascularization will still be required.

B. Endovascular Techniques

Pharmacomechanical thrombectomy catheters can achieve rapid revascularization and are most effective for the smaller arteries of the lower leg. Catheter-directed chemical thrombolysis into the clot with tissue plasminogen activator (TPA) may be done but often requires 24 hours or longer to fully lyse the thrombus. TPA can only be used in patients with mild ischemia, as determined by an intact neurologic examination. Patients with moderate to severe ischemia require immediate revascularization. Absolute contraindications for TPA include bleeding diathesis, GI bleeding, intracranial trauma, or neurosurgery within the past 3 months. Frequent vascular and access site examinations are required during the thrombolytic procedure to guard against the development of a hematoma.

C. Surgical Intervention

General anesthesia is usually indicated for surgical exploration of an acute arterial occlusion of a limb; local anesthesia may be used in extremely high-risk patients if the exploration is limited to the common femoral artery. In extreme cases, it may be necessary to perform thromboembolectomy from the femoral, popliteal, and even the pedal vessels to revascularize the limb. The combined use of devices that pulverize and aspirate clot and intraoperative thrombolysis with TPA improves outcomes.

Complications

Complications of revascularization of an acutely ischemic limb include severe metabolic acidosis, hyperkalemia, AKI, and cardiac arrest. When several hours have elapsed but recovery of viable tissue may still be possible, significant levels of lactic acid, potassium, and other harmful agents such as myoglobin may be released into the circulation during revascularization. Administering sodium bicarbonate (150 mEq $NaHCO_3$ in 1 L of dextrose 5% in water at a rate of 1–1.5 L in the first hour and then adjust the rate to manage acidosis) before reestablishing arterial flow is required. Surgery in the presence of thrombolytic agents and heparin carries a high risk of postoperative wound hematoma.

Prognosis

There is a 10–25% risk of amputation with an acute arterial embolic occlusion, and a 25% or higher in-hospital mortality rate. Prognosis for acute thrombotic occlusion of an atherosclerotic segment is generally better because the collateral flow can maintain extremity viability. The longer-term survival reflects the overall condition of the patient. In high-risk patients, an acute arterial occlusion is associated with a dismal prognosis.

OCCLUSIVE CEREBROVASCULAR DISEASE

ESSENTIALS OF DIAGNOSIS

- Sudden onset of weakness and numbness of an extremity or the face, aphasia, dysarthria, or unilateral blindness (amaurosis fugax).
- Bruit heard loudest in the mid neck.

General Considerations

Unlike the other vascular territories, symptoms of ischemic cerebrovascular disease are predominantly due to emboli. When collateral flow reestablishes perfusion, ischemia reverses (transient ischemic attacks [TIAs]) but signals a high risk for additional emboli and stroke. Most ischemic strokes are due to emboli from the heart. One-quarter of all ischemic strokes may be due to emboli from an arterial source; approximately 90% of these emboli originate from the proximal internal carotid artery, an area uniquely prone to the development of atherosclerosis. The aortic arch may also be an atheroembolic source. Intracranial atherosclerotic lesions are uncommon in western populations but are the most frequent location of cerebrovascular disease in Asian populations.

Clinical Findings

A. Symptoms and Signs

Generally, the symptoms of a TIA last only a few seconds to minutes (but may continue up to 24 hours) while a stroke is defined as persistent symptoms beyond 24 hours. The most common lesions associated with carotid disease involve the anterior circulation in the cortex with both motor and sensory involvement. Emboli to the retinal artery cause unilateral blindness; transient monocular blindness is termed "amaurosis fugax." Posterior circulation symptoms referable to the brainstem, cerebellum, and visual regions of the brain may be due to atherosclerosis of the vertebral basilar systems and are much less common.

Signs of cerebrovascular disease may include carotid artery bruits. However, there is poor correlation between the degree of stenosis and the presence of the bruit.

Furthermore, the presence of a bruit does not correlate with stroke risk. Nonfocal symptoms, such as dizziness and unsteadiness, seldom are related to cerebrovascular atherosclerosis.

B. Imaging

Duplex ultrasonography is the imaging modality of choice with high specificity and sensitivity for detecting and grading the degree of stenosis at the carotid bifurcation (see Chapter 24).

Excellent depiction of the full anatomy of the cerebrovascular circulation from aortic arch to cranium can be obtained with MRA or CTA. Each of the modalities may have false-positive or false-negative findings. Since the decision to intervene in cases of carotid stenosis depends on an accurate assessment of the degree of stenosis, it is recommended that at least two modalities be used to confirm the degree of stenosis. Diagnostic cerebral angiography is reserved when carotid artery stenting is planned or other imaging modalities are contraindicated.

Treatment

See Chapter 24 for a discussion of the medical management of occlusive cerebrovascular disease.

A. Asymptomatic Patients

Large studies have shown a 5-year reduction in stroke rate from 11.5% to 5.0% with surgical treatment of asymptomatic carotid stenosis that is greater than 60%; these patients with asymptomatic carotid stenosis may benefit from carotid intervention if their risk from intervention is low and their expected survival is longer than 5 years. Aggressive risk factor modification, including high-potency statins, may be as valuable as surgical intervention in these patients; the large NIH-sponsored CREST2 study is examining this issue.

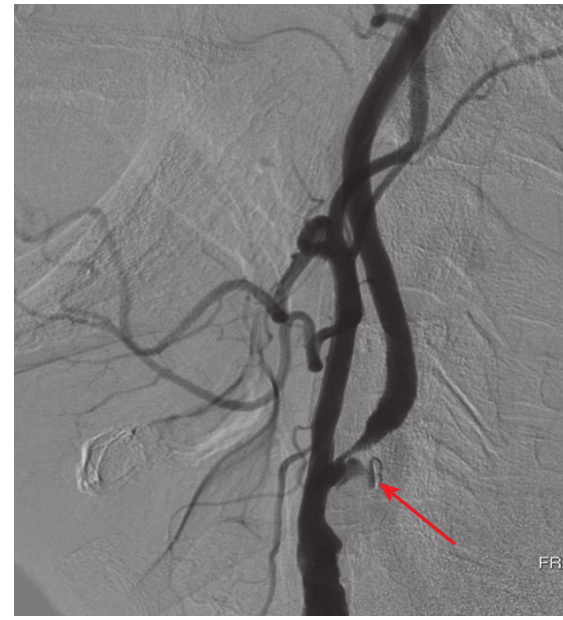
Mild to moderate disease (30–50% stenosis) indicates the need for ongoing monitoring and aggressive risk factor modification. Patients with carotid stenosis that suddenly worsens likely have an unstable plaque and are at particularly high risk for embolic stroke.

B. Symptomatic Patients

Large randomized trials have shown that patients with TIAs or strokes from which they have completely or nearly completely recovered will benefit from carotid intervention if the ipsilateral carotid artery has a stenosis of more than 70% (Figure 12–1), and they are likely to benefit if the artery has a stenosis of 50–69%. In these situations, carotid endarterectomy (CEA) and, in selected cases, carotid artery stenting, have been shown to have a durable effect in preventing further events. In symptomatic patients, intervention should ideally be planned within 2 weeks since delays increase the risk of a second event.

Complications

The most common complication from carotid intervention is cranial nerve injury, while the most dreaded complication is stroke from embolization or carotid occlusion.



▲ **Figure 12–1.** Digital subtraction angiography of a high-grade (90%) stenosis of the internal carotid artery with ulceration (arrow). (Used, with permission, from Dean SM, Satiani B, Abraham WT. *Color Atlas and Synopsis of Vascular Diseases.* McGraw-Hill, 2014.)

The American Heart Association's recommendations for upper limits of acceptable combined morbidity and mortality for these interventions is 3% for patients with asymptomatic carotid stenosis, 5% for those with TIAs, and 7% for patients with previous stroke. Higher rates of morbidity and mortality negate the therapeutic benefit of carotid intervention.

A. Carotid Endarterectomy

In the 2010 CREST study, the stroke risk for CEA was 2.3%. CEA also carries a 1–2% risk of permanent cranial nerve injury (usually the vagus nerve). A postoperative neck hematoma can cause acute airway compromise. CAD is a comorbidity in most of these patients. MI rates after CEA are approximately 2–6%.

B. Carotid Angioplasty and Stenting

Carotid artery stenting had a stroke risk of 4.1% in the 2010 CREST study; patients over 70 years of age and women had higher stroke rates with carotid artery stenting than with CEA. However, the risk of MI was lower with carotid artery stenting compared to CEA (1.1% vs 2.3%). Carotid artery stenting is indicated for reoperative cases, prior neck radiation, and high carotid bifurcations not otherwise accessible surgically. Nonetheless, emboli are more common during transfemoral carotid artery stenting in spite of embolic protection devices, especially when the carotid artery is heavily calcified. Transcervical carotid stenting, performed through a small incision at the base of the neck, avoids the aortic arch, uses cerebral protective flow reversal, and has lower reported embolization rates than transfemoral carotid stenting.

Prognosis

Twenty-five percent of patients with carotid stenosis and a TIA or small stroke will have further brain ischemia within 18 months with most of the events occurring within the first 6 months. Historically, patients with asymptomatic carotid stenosis likely had an annual stroke rate of just over 2% which may be lower in the statin era. Prospective ultrasound screening at least annually is recommended in asymptomatic patients with known carotid stenosis to identify plaque progression, which increases stroke risk. Concomitant CAD is common and is an important factor both for perioperative risk and long-term prognosis. Aggressive risk factor modification should be prescribed for patients with cerebrovascular disease regardless of planned intervention.

When to Refer

Both asymptomatic and symptomatic patients with a carotid stenosis of 70% or greater by ultrasound criteria and patients with carotid stenosis of 50% or greater with symptoms of a TIA or stroke should be referred to a vascular specialist for consultation.

When to Admit

Individuals with a TIA or stroke should be admitted for further workup and evaluation. Further imaging is warranted in these patients and anticoagulation with heparin should be initiated after ruling out hemorrhagic stroke.

Brott TG et al; CREST Investigators. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. N Engl J Med. 2016;374:1021. [PMID: 26890472]

Paraskevas KI et al. An updated systematic review and meta-analysis of results of transcervical carotid artery stenting with flow reversal. J Vasc Surg. 2020;72:1489. [PMID: 32422272]

VISCERAL ARTERY INSUFFICIENCY (Intestinal Angina)

ESSENTIALS OF DIAGNOSIS

- Severe postprandial abdominal pain.
- Weight loss with a "fear of eating."
- **Acute mesenteric ischemia:** severe abdominal pain yet minimal findings on physical examination.

General Considerations

Acute mesenteric ischemia results from occlusive mesenteric arterial disease, either embolic occlusion or primary thrombosis of at least one major mesenteric artery. Ischemia can also result from **nonocclusive mesenteric ischemia,** which is generally seen in patients with low flow states, such as severe heart failure, sepsis, or hypotension. **Chronic mesenteric ischemia,** also called intestinal angina, occurs when increased flow demands during feeding are not met resulting in abdominal pain. Because of the rich collateral mesenteric network, generally at least two of the three major visceral vessels (celiac, superior mesenteric, inferior mesenteric arteries) must be affected before symptoms develop. **Ischemic colitis,** a variant of mesenteric ischemia, usually occurs in the distribution of the inferior mesenteric artery. The intestinal mucosa is the most sensitive to ischemia and will slough if underperfused.

Clinical Findings

A. Symptoms and Signs

1. Acute mesenteric ischemia—Visceral arterial embolism presents acutely with severe abdominal pain. In contrast, patients with primary visceral arterial thrombosis often have an antecedent history consistent with chronic mesenteric ischemia. The key finding with acute mesenteric ischemia is severe, steady, diffuse abdominal pain with an absence of focal tenderness or distention. This "pain out of proportion" to physical examination findings occurs because ischemia initially is mucosal and does not impact the peritoneum until transmural ischemia inflames the peritoneal lining. A high WBC count, lactic acidosis, hypotension, and abdominal distention may aid in the diagnosis.

2. Chronic mesenteric ischemia—Patients are generally over 45 years of age and may have evidence of atherosclerosis in other vasculature. Symptoms consist of epigastric or periumbilical postprandial pain lasting 1–3 hours. To avoid the pain, patients limit food intake and may develop a fear of eating. Weight loss is universal. In severe cases of intestinal angina, patients may become dehydrated, which can cause hypotension and an acute thrombosis.

3. Ischemic colitis—Characteristic symptoms are left lower quadrant pain and tenderness, abdominal cramping, and mild diarrhea (non-bloody or bloody). Rectal discharge will appear mucus-like or bloody and should prompt further evaluation.

B. Imaging and Colonoscopy

Contrast-enhanced CT is accurate at determining the presence of ischemic intestine. In acute or chronic mesenteric ischemia, a CTA or MRA can demonstrate narrowing of the proximal visceral vessels. In acute mesenteric ischemia from a nonocclusive low flow state, angiography is needed to display the typical "pruned tree" appearance of the distal visceral vascular bed. Ultrasound scanning of the mesenteric vessels may show proximal obstructing lesions.

In patients with ischemic colitis, flexible sigmoidoscopy should be performed to assess the grade of ischemia that occurs most often in watershed areas, such as the rectal sigmoid and splenic flexure.

Treatment

1. Acute mesenteric ischemia—A high suspicion of acute mesenteric ischemia dictates immediate exploration to assess bowel viability. If the bowel remains viable, arterial bypass using a prosthetic conduit can be done either from

the supra-celiac aorta or common iliac artery to the celiac and the superior mesentery artery. Angioplasty and stenting of the arteries can be used but do not avoid a surgical evaluation of bowel viability.

2. Chronic mesenteric ischemia—Angioplasty and stenting of the proximal vessel may be beneficial depending on the anatomy of the stenosis. Should an endovascular solution not be available, an aorto-visceral artery bypass is the preferred management. The long-term results are highly durable.

3. Ischemic colitis—The mainstay of treatment is maintenance of blood pressure and perfusion until collateral circulation becomes well established. The patient must be monitored closely for evidence of perforation necessitating resection.

Prognosis

The combined morbidity and mortality rates are 10–15% from surgical intervention of chronic mesenteric ischemia, in part due to patients' malnutrition and frailty. The combined morbidity and mortality rates from surgical intervention of acute mesenteric ischemia is 50–69%, although only 25% of patients will survive 1 year. However, without intervention, both acute and chronic mesenteric ischemia are uniformly fatal. Adequate collateral circulation usually develops in those who have ischemic colitis, and the prognosis for this entity is better than chronic mesenteric ischemia.

When to Refer

Any patient in whom there is a suspicion of mesenteric ischemia should be urgently referred for imaging and possible intervention.

When to Admit

Indications for admission include the presence of abdominal pain out of proportion to abnormal physical findings (there are no findings of peritonitis and the abdomen is soft) or a history of worsening intestinal angina with inability to tolerate a diet.

Alahdab F et al. A systematic review and meta-analysis of endovascular versus open surgical revascularization for chronic mesenteric ischemia. J Vasc Surg. 2018;67:1598. [PMID: 29571626]

Lim S et al. Contemporary management of acute mesenteric ischemia in the endovascular era. Vasc Endovascular Surg. 2019;53:42. [PMID: 30360689]

ACUTE MESENTERIC VEIN OCCLUSION

The hallmarks of acute mesenteric vein occlusion are postprandial pain and evidence of a hypercoagulable state. Acute mesenteric vein occlusion presents similarly to the arterial occlusive syndromes but is much less common. Patients at risk include those with paroxysmal nocturnal hemoglobinuria; protein C, protein S, or antithrombin deficiencies; or the *JAK2* mutation. Thrombolysis is the mainstay of therapy. Aggressive long-term anticoagulation is required.

NONATHEROSCLEROTIC VASCULAR DISEASE

THROMBOANGIITIS OBLITERANS (Buerger Disease)

ESSENTIALS OF DIAGNOSIS

- Typically occurs in male cigarette smokers.
- Distal extremities involved with severe ischemia, progressing to tissue loss.
- Thrombosis of the superficial veins may occur.
- Smoking cessation is essential to stop disease progression.

General Considerations

Thromboangiitis obliterans (Buerger disease) is a segmental, inflammatory, and thrombotic process of the distalmost arteries and occasionally veins of the extremities. Pathologic examination reveals arteritis in the affected vessels. The cause is not known but it is rarely seen in patients who do not smoke cigarettes. Arteries most commonly affected are the plantar and digital vessels of the foot and lower leg. In advanced stages, the fingers and hands may become involved. The incidence of thromboangiitis obliterans has decreased dramatically.

Clinical Findings

A. Symptoms and Signs

Thromboangiitis obliterans may be initially difficult to differentiate from atherosclerotic peripheral vascular disease, but in most cases, the lesions are on the toes and the patient is younger than 40 years. The observation of superficial thrombophlebitis may aid the diagnosis. Because the distal vessels are usually affected, intermittent claudication is not common, but rest pain, particularly pain in the distal most extremity (ie, toes), is frequent. This pain often progresses to tissue loss and amputation unless the patient stops smoking. The progression of the disease seems to be intermittent with acute and dramatic episodes followed by some periods of remission.

B. Imaging

MRA or invasive angiography can demonstrate the obliteration of the distal arterial tree typical of thromboangiitis obliterans.

Differential Diagnosis

In atherosclerotic peripheral vascular disease, the onset of tissue ischemia tends to be less dramatic than in thromboangiitis obliterans, and symptoms of proximal arterial involvement, such as claudication, predominate.

Symptoms of Raynaud disease may be difficult to differentiate from thromboangiitis obliterans and may coexist

in 40% of patients. Repetitive atheroemboli may also mimic thromboangiitis obliterans. It may be necessary to image the proximal arterial tree to rule out sources of arterial microemboli.

Treatment

Cessation of cigarette smoking is the mainstay of therapy and will halt the disease in most cases. As the distal arterial tree is occluded, revascularization is often not possible. Intra-arterial infusion of prostacyclin analogs has been reported to improve ulcer healing in select cases. Sympathectomy is rarely effective.

Prognosis

If smoking cessation can be achieved, the outlook for thromboangiitis obliterans may be better than in patients with premature peripheral vascular disease. If smoking cessation is not achieved, then the prognosis is generally poor, with amputation of both lower and upper extremities a possible outcome.

Cacione DG et al. Pharmacological treatment for Buerger's disease. Cochrane Database Syst Rev. 2020;5:CD011033. [PMID: 32364620]

ARTERIAL ANEURYSMS

ABDOMINAL AORTIC ANEURYSM

ESSENTIALS OF DIAGNOSIS

- Most aortic aneurysms are asymptomatic until rupture.
- 80% of AAAs measuring 5 cm are palpable; the usual threshold for treatment is 5.5 cm.
- Back or abdominal pain with aneurysmal tenderness may precede rupture.
- Rupture is catastrophic: excruciating abdominal pain that radiates to the back; hypotension.

General Considerations

Dilatation of the infrarenal aorta is a normal part of aging. The aorta of a healthy young man measures approximately 2 cm. An aneurysm is considered present when the aortic diameter exceeds 3 cm, but aneurysms rarely rupture until their diameter exceeds 5 cm. AAAs are found in 2% of men over 55 years of age; the male to female ratio is 4:1. Ninety percent of abdominal atherosclerotic aneurysms originate below the renal arteries. The aneurysms usually involve the aortic bifurcation and often involve the common iliac arteries.

Aortic inflammation is uncommon with atherosclerotic aneurysms and may be due to inflammation from aortic vasculitis, as in Takayasu disease or Behçet disease. Rarely, inflammatory aortitis is due to infections, including *Salmonella,* tuberculosis, and syphilis. Periaortic inflammation without vasculitis or infection (inflammatory aneurysm) is due to retroperitoneal fibrosis, either idiopathic or secondary (IgG_4-related disease).

Clinical Findings

A. Symptoms and Signs

1. Asymptomatic—Although 80% of 5-cm infrarenal aneurysms are palpable on routine physical examination, most aneurysms are discovered on ultrasound or CT imaging as part of a screening program or during the evaluation of unrelated abdominal symptoms.

2. Symptomatic—

A. Pain—Aneurysmal expansion may be accompanied by pain that is mild to severe midabdominal discomfort often radiating to the lower back. The pain may be constant or intermittent and is exacerbated by even gentle pressure on the aneurysm sack. Pain may also accompany inflammatory aneurysms. Most aneurysms have a thick layer of thrombus lining the aneurysmal sac, but embolization to the lower extremities is rarely seen.

B. Rupture—The sudden escape of blood into the retroperitoneal space causes severe pain and hypotension. Free rupture into the peritoneal cavity is a lethal event.

B. Laboratory Findings

In acute cases of a contained retroperitoneal rupture, the hematocrit may be normal, since there has been no opportunity for hemodilution.

Patients with aneurysms may also have CAD, carotid disease, kidney disease, and emphysema, which are typically seen in elderly men who smoke cigarettes. Preoperative testing may indicate the presence of these comorbid conditions, which increase the risk of intervention.

C. Imaging

Abdominal ultrasonography is the diagnostic study of choice for initial screening for the presence of an aneurysm. In approximately three-quarters of patients with aneurysms, curvilinear calcifications outlining portions of the aneurysm wall may be visible on plain radiographs of the abdomen or back. CT scans provide a more reliable assessment of aneurysm diameter and should be done when the aneurysm nears the diameter threshold (5.5 cm) for treatment. Contrast-enhanced CT scans show the arteries above and below the aneurysm. CT imaging will often demonstrate mural thrombus within the aneurysm and is not an indication for anticoagulation.

Once an aneurysm is identified, routine follow-up with ultrasound will determine size and growth rate. The frequency of imaging depends on aneurysm size ranging from every 2 years for aneurysms smaller than 4 cm to every 6 months for aneurysms at or approaching 5 cm. When an aneurysm measures approximately 5 cm, a CTA with contrast should be done to more accurately assess the size of the aneurysm and define the anatomy.

Screening

Guidelines recommend abdominal ultrasound screening in men 65–75 years old with exposure to 100 or more lifetime cigarettes but conflict on whether women with the same exposure should be screened. Guidelines do not recommend repeated screening if the aorta shows no enlargement. While patients are monitored, smoking cessation and treatment of underlying hypertension, hyperlipidemia, and diabetes should be considered.

Treatment

A. Elective Repair

The risk of rupture increases with aneurysm diameter. In general, elective repair is indicated for aortic aneurysms 5.5 cm or larger in diameter or aneurysms that demonstrate rapid expansion (more than 0.5 cm in 6 months). Symptoms such as pain or tenderness may indicate impending rupture and require urgent repair regardless of the aneurysm's diameter.

B. Aneurysmal Rupture

A ruptured aneurysm is a lethal event. Approximately half the patients exsanguinate prior to reaching a hospital. In the remainder, bleeding may be temporarily contained in the retroperitoneum (contained rupture), allowing the patient to undergo emergent surgery. However, only half of those patients will survive. Endovascular repair is recommended for ruptured aneurysm treatment, with the results offering improvement over open repair for these critically ill patients.

C. Aortic Inflammation/Inflammatory Aneurysm

Aortic or periaortic inflammation requires medical treatment for the underlying cause (vasculitis, infection, or retroperitoneal fibrosis). Indications for surgical treatment are based on the size of the aneurysm (5.5 cm or larger), associated compression of retroperitoneal structures (such as the ureter), or pain upon palpation of the aneurysm. Interestingly, the inflammation that encases an inflammatory aneurysm recedes after either endovascular or open surgical aneurysm repair.

D. Assessment of Operative Risk

Aneurysms appear to be a variant of systemic atherosclerosis. Patients with aneurysms have a high rate of coronary disease, but a 2004 trial demonstrated minimal value in addressing stable CAD prior to aneurysm resection. However, in patients with significant symptoms of coronary disease, the coronary disease should be treated first. Aneurysm repair should follow shortly thereafter because there is a slightly increased risk of aneurysm rupture after the coronary procedures.

E. Open Surgical Resection Versus Endovascular Repair

In open surgical aneurysm repair, a graft is sutured to the nondilated vessels above and below the aneurysm. This involves an abdominal incision, extensive dissection, and interruption of aortic blood flow. The mortality rate is low (2–5%) in centers that have a high volume for this procedure and when it is performed in good-risk patients. Older, sicker patients may not tolerate the cardiopulmonary stresses of the operation. With endovascular aortic repair, a stent-graft is introduced through small incisions over the femoral arteries and positioned within the aorta under fluoroscopic guidance. The stent must be able to seal securely against the wall of the aorta above and below the aneurysm, thereby excluding blood from flowing into the aneurysm sac. To successfully treat an aneurysm, the anatomic requirements for endovascular repairs are more precise than for open repairs. Most studies have found that endovascular aortic repair offers patients reduced operative morbidity and mortality as well as shorter recovery periods. Long-term survival is equivalent between the two techniques. Patients who undergo endovascular repair, however, likely need additional interventions and need lifelong monitoring, since there is a 10–15% incidence of continued aneurysm growth after endovascular repair.

Complications

MI, the most common complication, occurs in up to 10% of patients who undergo open aneurysm repair. The incidence of MI is substantially lower with endovascular repair. For routine infrarenal aneurysms, renal injury is unusual; however, when it does occur, or if the baseline creatinine is elevated, it is a significant complicating factor in the postoperative period. Respiratory complications are similar to those seen in most major abdominal surgery. GI hemorrhage, even years after aortic surgeries, suggests the possibility of **graft enteric fistula,** most commonly between the aorta and the distal duodenum; the incidence of this complication is higher when the initial surgery is performed on an emergency basis.

Prognosis

The mortality rate for an open elective surgical resection is 1–5%, and the mortality rate for endovascular therapy is 0.5–2%. Of those who survive surgery, approximately 60% are alive at 5 years; MI is the leading cause of death. The long-term survival (5 years or more) after open and endovascular repairs is equivalent.

Mortality rates of untreated aneurysms vary with aneurysm diameter. The mortality rate among patients with large aneurysms has been defined as follows: 12% annual risk of rupture with an aneurysm larger than 6 cm in diameter and a 25% annual risk of rupture in aneurysms of more than 7 cm diameter. In general, a patient with an aortic aneurysm larger than 5.5 cm has a threefold greater chance of dying of a consequence of rupture of the aneurysm than of dying of the surgical resection.

At present, endovascular aneurysm repair may be less definitive than open surgical repair and requires close follow up with an imaging procedure. Device migration, component separation, and graft limb thrombosis or kinking are common reasons for repeat intervention. With complete exclusion of blood from the aneurysm sac, the

pressure is lowered, which causes the aneurysm to shrink. An "endoleak" from the top or bottom seal zones (type 1) or through a graft defect (type 3) is associated with a persistent risk of rupture. Indirect leakage of blood through lumbar and inferior mesenteric branches of the aneurysm (type-2 endoleak) produces an intermediate picture with somewhat reduced pressure in the sac, slow shrinkage, and low rupture risk. However, type-2 endoleak warrants close observation as aneurysm dilatation can change aneurysm morphology leading to type-1 endoleak and rupture.

When to Refer

- Any patient with a 4.5-cm or larger aortic aneurysm should be referred to a vascular specialist for observation and assessment.
- Urgent referrals should be made if the patient complains of pain and gentle palpation of the aneurysm confirms that it is the source, regardless of the aneurysmal size.

When to Admit

- Patients with a tender aneurysm to palpation or signs of aortic rupture require emergent hospital admission.
- Evidence of infection after repair.

O'Donnell TFX et al. Abdominal aortic aneurysm screening guidelines: United States Preventive Services Task Force and Society for Vascular Surgery. J Vasc Surg. 2020;71:1457. [PMID: 32334726]
Jin J. Screening for abdominal aortic aneurysm. JAMA Patient Page. JAMA. 2019;322:2256. [PMID: 31821432]
Lederle FA et al; OVER Veterans Affairs Cooperative Study Group. Open versus endovascular repair of abdominal aortic aneurysm. N Engl J Med. 2019;380:2126. [PMID: 31141634]
Schanzer A et al. Management of abdominal aortic aneurysms. N Engl J Med. 2021;385:1690. [PMID: 34706173]

THORACIC AORTIC ANEURYSMS

ESSENTIALS OF DIAGNOSIS

- Widened mediastinum on chest radiograph.
- With rupture, sudden onset of chest pain radiating to the back.

General Considerations

Most thoracic aortic aneurysms are due to atherosclerosis; syphilis is a rare cause. Disorders of connective tissue and Ehlers-Danlos and Marfan syndromes also are rare causes but have important therapeutic implications. Traumatic, false aneurysms, caused by partial tearing of the aortic wall with deceleration injuries, may occur just beyond the origin of the left subclavian artery. Less than 10% of aortic aneurysms occur in the thoracic aorta.

Clinical Findings

A. Symptoms and Signs

Most thoracic aneurysms are asymptomatic. When symptoms occur, they depend largely on the size and the position of the aneurysm and its rate of growth. Substernal back or neck pain may occur. Pressure on the trachea, esophagus, or superior vena cava can result in the following symptoms and signs: dyspnea, stridor or brassy cough, dysphagia, and edema in the neck and arms as well as distended neck veins. Stretching of the left recurrent laryngeal nerve causes hoarseness. With aneurysms of the ascending aorta, aortic regurgitation may be present due to dilation of the aortic valve annulus. Rupture of a thoracic aneurysm is catastrophic because bleeding is rarely contained, allowing no time for emergent repair.

B. Imaging

The aneurysm may be diagnosed on chest radiograph by the calcified outline of the dilated aorta. CT scanning with contrast enhancement is the modality of choice, but MRA can be used to demonstrate the anatomy and aneurysmal size and to exclude lesions that can mimic aneurysms, such as neoplasms or substernal goiter. There is no low-cost alternative (eg, ultrasonography) for screening or surveillance. Cardiac catheterization and echocardiography may be required to describe the relationship of the coronary vessels to an aneurysm of the ascending aorta.

Treatment

Indications for repair depend on the location of dilation, rate of growth, associated symptoms, and overall condition of the patient. Aneurysms that involve the proximal aortic arch or ascending aorta represent particularly challenging problems and may be considered for repair when they measure 5.5 cm. Open surgery is usually required, carrying substantial risk of morbidity (including stroke, diffuse neurologic injury, and intellectual impairment) because interruption of arch blood flow is required. Descending thoracic aneurysms measuring 5.5 cm or larger should be considered for repair, since there is a 5-year survival of 54% in untreated patients. Aneurysms of the descending thoracic aorta are treated routinely by endovascular grafting. Repair of aortic arch aneurysms should be undertaken only if there is a skilled surgical team with an acceptable record of outcomes for these complex procedures. The availability of thoracic aortic endograft technique using complex branched endovascular reconstructions for aneurysms involving the arch or visceral aorta (custom-made grafts with branches to the vessels involved in the aneurysm) does not change the indications for aneurysm repair.

Complications

With the exception of endovascular repair for discrete saccular aneurysms of the descending thoracic aorta, the morbidity and mortality of thoracic aneurysm repair is higher than for infra-renal AAA repair. Paraplegia remains a devastating complication. Most large series

report approximately 4–10% rate of paraplegia following endovascular repair of thoracic aortic aneurysms. The spinal arterial supply is segmental through intercostal branches of the aorta with variable degrees of intersegmental connection. Therefore, the more extensive the aneurysm, the greater is the risk of paraplegia with repair. Prior infrarenal abdominal aortic surgery, subclavian or internal iliac artery occlusion, and hypotension all increase the paraplegia risk. Involvement of the aortic arch also increases the risk of stroke, even when the aneurysm does not directly affect the carotid artery.

Prognosis

Generally, degenerative aneurysms of the thoracic aorta will enlarge (on average 0.1 cm/y) and require repair to prevent death from rupture. Saccular aneurysms, particularly those distal to the left subclavian artery and the descending thoracic aorta, have good results with endovascular repair. Resection of aneurysms of the aortic arch requires a skilled surgical team and should be attempted only in low-risk patients. Branched or fenestrated endovascular grafting technology has demonstrated reduced morbidity and mortality.

When to Refer

- Ascending aortic aneurysms larger than 4.5 cm should be referred to a cardiac surgeon for observation and assessment and considered for repair at 5.5 cm.
- Descending thoracic aortic aneurysm should be referred to a vascular specialist when they reach 5 cm for observation and assessment and considered for repair at 5.5 cm.

When to Admit

- Any patient with chest or back pain with a known or suspected thoracic aorta aneurysm must be brought to the hospital and undergo urgent imaging studies to rule out the aneurysm as a cause of the pain.

Tenorio ER et al. Endovascular repair for thoracoabdominal aortic aneurysms: current status and future challenges. Ann Cardiothorac Surg. 2021;10:744. [PMID: 34926178]

Upchurch GR et al. Society for Vascular Surgery clinical practice guidelines of thoracic endovascular aortic repair for descending thoracic aortic aneurysms. J Vasc Surg. 2021;73:55S. [PMID: 32628988]

PERIPHERAL ARTERY ANEURYSMS

ESSENTIALS OF DIAGNOSIS

- Widened, prominent pulses.
- Acute leg or foot pain and paresthesias with loss of distal pulses.
- High association of popliteal aneurysms with AAAs.

General Considerations

Like aortic aneurysms, peripheral artery aneurysms are silent until critically symptomatic. However, unlike aortic aneurysms, the presenting manifestations are due to peripheral embolization and thrombosis. Popliteal artery aneurysms account for 70% of peripheral arterial aneurysms. Popliteal aneurysms may embolize repetitively over time and occlude distal arteries. Due to the redundant parallel arterial supply to the foot, ischemia does not occur until a final embolus occludes flow.

Primary femoral artery aneurysms are much less common. However, pseudoaneurysms of the femoral artery following arterial punctures for arteriography and cardiac catheterization occur with an incidence ranging from 0.05% to 6% of arterial punctures.

Clinical Findings

A. Symptoms and Signs

The patient may be aware of a pulsatile mass when the aneurysm is in the groin, but popliteal aneurysms are often undetected by the patient and clinician. Rarely, peripheral aneurysms may produce symptoms by compressing the local vein or nerve. The first symptom may be due to ischemia of acute arterial occlusion. The symptoms range from sudden-onset pain and paralysis to short-distance claudication that slowly lessens as collateral circulation develops. Symptoms from recurrent embolization to the leg are often transient, if they occur at all. Sudden ischemia may appear in a toe or part of the foot, followed by slow resolution, and the true diagnosis may be elusive. The onset of recurrent episodes of pain in the foot, particularly if accompanied by cyanosis, suggests embolization and requires investigation of the heart and proximal arterial tree.

Because popliteal pulses are somewhat difficult to palpate even in normal individuals, a particularly prominent or easily felt pulse is suggestive of aneurysm and should be investigated by ultrasound. Since popliteal aneurysms are bilateral in 60% of cases, the diagnosis of thrombosis of a popliteal aneurysm is often aided by the palpation of a pulsatile aneurysm in the contralateral popliteal space. Approximately 50% of patients with popliteal aneurysms have an aneurysmal abdominal aorta.

B. Imaging Studies

Duplex color ultrasound is the most efficient investigation to confirm the diagnosis of peripheral aneurysm, measure its size and configuration, and demonstrate mural thrombus. MRA or CTA is required to define the aneurysm and local arterial anatomy for reconstruction. Arteriography is not recommended because mural thrombus reduces the apparent diameter of the lumen on angiography. Patients with popliteal aneurysms should undergo abdominal ultrasonography to determine whether an AAA is also present.

Treatment

To prevent limb loss, immediate or urgent surgery is indicated when acute embolization or thrombosis has caused

acute ischemia. Open surgical bypass is generally indicated. Similarly, surgery is indicated when an aneurysm is associated with any peripheral embolization, the aneurysm is larger than 2 cm, or a mural thrombus is present. Endovascular exclusion of the aneurysm can be done but has anatomic constraints and is reserved for high-risk patients. Intra-arterial thrombolysis may be done in the setting of acute ischemia, if examination (light touch) remains intact, suggesting that immediate surgery is not imperative. Acute pseudoaneurysms of the femoral artery due to arterial punctures can be successfully treated using ultrasound-guided compression or thrombin injection. Open surgery with prosthetic interposition grafting is preferred for primary aneurysms of the femoral artery.

Prognosis

Approximately one-third of untreated patients will require an amputation. The long-term patency of bypass grafts for femoral and popliteal aneurysms is generally excellent but depends on the adequacy of the outflow tract. Late graft occlusion is less common than in similar surgeries for occlusive disease.

When to Refer

- Peripheral arterial aneurysms measuring 2 cm or with ultrasound evidence of thrombus within the aneurysm should be referred to a vascular specialist.

When to Admit

Patients with symptoms of ischemia or any signs of embolization should be admitted.

AORTIC DISSECTION

ESSENTIALS OF DIAGNOSIS

- Sudden searing chest pain with radiation to the back, abdomen, or neck in a hypertensive patient.
- Widened mediastinum on chest radiograph.
- Pulse discrepancy in the extremities.
- Acute aortic regurgitation may develop.

General Considerations

Aortic dissection occurs when a spontaneous intimal tear develops and blood dissects into the media of the aorta. The tear can result from repetitive torque applied to the ascending and proximal descending aorta during the cardiac cycle; hypertension is an important component of this disease process. Dissections are classified by the entry point and distal extent. **Type A dissection** involves the arch proximal to the left subclavian artery, and **type B dissection** occurs in the proximal descending thoracic aorta typically just beyond the left subclavian artery. Dissections may occur in the absence of hypertension but abnormalities of smooth muscle, elastic tissue, or collagen are more common in these patients. Pregnancy, bicuspid aortic valve, and coarctation also are associated with increased risk of dissection.

Blood entering the intimal tear may extend the dissection into the abdominal aorta, the lower extremities, the carotid arteries, or less commonly, the subclavian arteries. Both absolute pressure levels and the pulse pressure are important in propagation of dissection. *Aortic dissection is a true emergency and requires immediate control of blood pressure to limit the extent of the dissection.* With type A dissection, which has the worse prognosis, death may occur within hours due to rupture of the dissection into the pericardial sac or dissection into the coronary arteries, resulting in MI. Rupture into the pleural cavity is also possible. The intimal/medial flap of the aortic wall created by the dissection may occlude major aortic branches, resulting in ischemia of the brain, intestines, kidney, or extremities.

Clinical Findings

A. Symptoms and Signs

Severe persistent chest pain of sudden onset radiating down the back or possibly into the anterior chest is characteristic. Radiation of the pain into the neck may also occur. The patient is usually hypertensive. Syncope, hemiplegia, or paralysis of the lower extremities may occur. Mesenteric ischemia or kidney injury may develop. Peripheral pulses may be diminished or unequal. A diastolic murmur may develop as a result of a dissection in the ascending aorta close to the aortic valve, causing valvular regurgitation, heart failure, and cardiac tamponade.

B. Electrocardiographic Findings

LVH from long-standing hypertension is often present. Acute changes suggesting myocardial ischemia do not develop unless dissection involves the coronary artery ostium. Classically, inferior wall abnormalities predominate since dissection leads to compromise of the right rather than the left coronary artery. In some patients, the ECG may be completely normal.

C. Imaging

A multiplanar CT scan with contrast enhancement is the immediate diagnostic imaging modality of choice; clinicians should have a low threshold for obtaining a CT scan in any hypertensive patient with chest pain and equivocal findings on ECG. The CT scan should include both the chest and abdomen to fully delineate the extent of the dissected aorta. MRA is an excellent imaging modality for chronic dissections, but in the acute situation, the longer imaging time and the difficulty of monitoring patients in the MRI scanner make the CT scan preferable. Chest radiographs may reveal an abnormal aortic contour or widened superior mediastinum. Although transesophageal echocardiography (TEE) is an excellent diagnostic imaging method, it is generally not readily available in the acute setting.

Differential Diagnosis

Aortic dissection is most commonly misdiagnosed as MI or other causes of chest pain such as pulmonary

embolization. Dissections may occur with minimal pain; branch vessel occlusion of the lower extremity can mimic arterial embolus.

Treatment

A. Medical

Aggressive measures to lower blood pressure should occur when an aortic dissection is suspected, even before the diagnostic studies have been completed. Treatment requires a simultaneous reduction of the systolic blood pressure to 100–120 mm Hg and heart rate to 60–70 beats/minute. Beta-blockers should be first-line therapy because they reduce the LV ejection force that weakens the arterial wall. Labetalol, both an alpha- and beta-blocker, lowers heart rate and achieves rapid blood pressure control. Give 20 mg over 2 minutes by intravenous injection. Additional doses of 40–80 mg intravenously can be given every 10 minutes (maximum dose 300 mg) until the desired blood pressure has been reached. Alternatively, 2 mg/minute may be given by intravenous infusion, titrated to desired effect. The short half-life of esmolol allows for rapid titration and for testing a patient's reaction to a beta-blocker if there are concerns about asthma or bradycardia. Give a loading dose of esmolol, 0.5 mg/kg intravenously over 1 minute, followed by an infusion of 0.0025–0.02 mg/kg/minute. Titrate the infusion to a goal heart rate of 60–70 beats/minute. For patients who cannot tolerate a beta-blocker or who need a second agent to control the hypertension, intravenous calcium channel blocker infusions, such as nicardipine, are an alternative. Start nicardipine 5 mg/hour intravenously and titrate the infusion to the desired effect. If beta-blockade alone does not control the hypertension, nitroprusside may be added as follows: 50 mg of nitroprusside in 1000 mL of 5% dextrose and water, infused at a rate of 0.5 mL/minute for a 70-kg person (0.3 mcg/kg/minute); the infusion rate is increased by 0.5 mL every 5 minutes until adequate control of the pressure has been achieved. Morphine sulfate is the appropriate drug to use for pain relief. Long-term medical care of patients should include beta-blockers in their antihypertensive regimen.

B. Surgical Intervention

1. Type A dissection—*Urgent surgical intervention is required for all type A dissections.* If a skilled cardiovascular team is not available, the patient should be transferred to an appropriate facility. The procedure involves grafting and replacing the diseased portion of the arch and brachiocephalic vessels as necessary. Replacement of the aortic valve may be required with reattachment of the coronary arteries.

2. Type B dissection with malperfusion—*Urgent surgery is required for type B dissections if there is aortic branch compromise resulting in malperfusion of the renal, visceral, or extremity vessels.* The immediate goal of surgery is to restore flow to the ischemic tissue. Endovascular stenting of the entry tear at the level of the subclavian artery may result in obliteration of the false lumen and restore flow into the branch vessel from the true lumen. The results, however, are unpredictable and should only be attempted by an experienced team.

3. Type B dissection without malperfusion—For acute type B dissections without malperfusion, blood pressure control is the primary treatment. Long-term aortic-specific survival and late aneurysm formation rates are improved with early thoracic stent graft repair, especially in healthy patients with high-risk anatomic features (aortic diameter greater than 4 cm or partial false lumen thrombosis).

Prognosis & Follow-Up

The mortality rate for untreated type A dissections is approximately 1% per hour for 72 hours and over 90% at 3 months. Mortality is also extremely high for untreated type B dissections with malperfusion or rupture. The surgical and endovascular therapies for these patients are technically demanding and require an experienced team to achieve perioperative mortalities of less than 10%. Aneurysmal enlargement of the residual false lumen may develop despite adequate antihypertensive therapy. Yearly CT scans are required to monitor for aneurysm development. Indications for late aneurysm repair are determined by aneurysm size (6 cm or larger), similar to undissected thoracic aneurysms.

When to Admit

- All patients with an acute dissection should be hospitalized for blood pressure management and observation.
- Urgent surgical repair is indicated for all type A dissections and for type B dissections with malperfusion, rupture, or persistent symptoms.

Bossone E et al. Epidemiology and management of aortic disease: aortic aneurysms and acute aortic syndromes. Nat Rev Cardiol. 2021;18:331. [PMID: 33353985]

VENOUS DISEASES

VARICOSE VEINS

ESSENTIALS OF DIAGNOSIS

- Dilated, tortuous superficial veins in the legs.
- Asymptomatic or aching discomfort or pain.
- Often hereditary.
- Increased frequency after pregnancy.

General Considerations

Varicose veins develop in the lower extremities. Periods of high venous pressure related to prolonged standing or heavy lifting are contributing factors, but the highest incidence occurs in women after pregnancy. Varicosities develop in over 20% of all adults.

The combination of progressive venous reflux and venous hypertension is the hallmark of chronic venous disease. The superficial veins are involved, typically the great saphenous vein and its tributaries, but the short saphenous vein (posterior lower leg) may also be affected. Distention of the vein prevents the valve leaflets from coapting, creating incompetence and reflux of blood toward the foot.

Secondary varicosities can develop as a result of obstructive changes and valve damage in the deep venous system following thrombophlebitis, or rarely as a result of proximal venous occlusion due to neoplasm or fibrosis. Congenital or acquired arteriovenous fistulas or venous malformations are also associated with varicosities and should be considered in young patients with varicosities.

Clinical Findings

A. Symptoms and Signs

Symptom severity is not correlated with the number and size of the varicosities; extensive varicose veins may produce no subjective symptoms, whereas minimal varicosities may produce many symptoms. Dull, aching heaviness or a feeling of fatigue of the legs brought on by periods of standing is the most common complaint. Itching from venous eczema may occur either above the ankle or directly overlying large varicosities.

Dilated, tortuous veins of the thigh and calf are visible and palpable when the patient is standing. Longstanding varicose veins may progress to chronic venous insufficiency with associated ankle edema, brownish skin hyperpigmentation, and chronic skin induration or fibrosis. A bruit or thrill is never found with primary varicose veins and, when found, alerts the clinician to the presence of an arteriovenous fistula or malformation.

B. Imaging

The identification of the source of venous reflux that feeds the symptomatic veins is necessary for effective surgical treatment. Duplex ultrasonography by a technician experienced in the diagnosis and localization of venous reflux is the test of choice for planning therapy. In most cases, reflux will arise from the greater saphenous vein.

Differential Diagnosis

Varicose veins due to primary superficial venous reflux should be differentiated from those secondary to previous or ongoing obstruction of the deep veins (post-thrombotic syndrome). Pain or discomfort secondary to neuropathy should be distinguished from symptoms associated with coexistent varicose veins. Similarly, vein symptoms should be distinguished from pain due to intermittent claudication, which occurs after a predictable amount of exercise and resolves with rest. In adolescent patients with varicose veins, imaging of the deep venous system is obligatory to exclude a congenital malformation or atresia of the deep veins. *Surgical treatment of varicose veins in these patients is contraindicated because the varicosities may play a significant role in venous drainage of the limb.*

Complications

Superficial thrombophlebitis of varicose veins is uncommon. The typical presentation is acute localized pain with tender, firm veins. The process is usually self-limiting, resolving within several weeks. The risk of DVT or embolization is very low unless the thrombophlebitis extends into the great saphenous vein in the upper medial thigh. Predisposing conditions include pregnancy, local trauma, or prolonged periods of sitting.

In older patients, superficial varicosities may bleed with even minor trauma. The amount of bleeding can be alarming as the pressure in the varicosity is high.

Treatment

A. Nonsurgical Measures

Nonsurgical treatment is effective. Elastic graduated compression stockings (20–30 mm Hg pressure) reduce the venous pressure in the leg and may prevent the progression of disease. Good control of symptoms can be achieved when stockings are worn daily during waking hours and legs are elevated, especially at night. Compression stockings are well-suited for elderly patients or patients who do not want surgery.

B. Varicose Vein Sclerotherapy

Direct injection of a sclerosing agent induces permanent fibrosis and obliteration of the target veins. Chemical irritants (eg, glycerin) or hypertonic saline are often used for small, less-than-4-mm reticular veins or telangiectasias. Foam sclerotherapy is used to treat the great saphenous vein, varicose veins larger than 4 mm, and perforating veins. Sclerotherapy of varicose veins without treatment of underlying saphenous vein reflux is associated with varicosity recurrence rates over 50% as uncorrected reflux progressively dilates adjacent veins. Complications such as phlebitis, tissue necrosis, or infection may occur with any sclerosing agent.

C. Surgical Reflux Treatment

Treatment options for reflux arising from the great saphenous vein include surgical vein stripping (removal) or endovenous treatments using thermal devices (laser or radiofrequency catheter), cyanoacrylate glue injection, or foam sclerosant injection. Endovenous treatments can often be performed with local anesthesia alone and the early success is equal to vein stripping. Long-term success is highest with vein stripping and thermal treatments while the long-term durability of cyanoacrylate glue and foam is unknown. One major complication of thermal treatments is endothermal heat-induced thrombosis of the deep vein and may require prolonged anticoagulation. Less common sources of reflux include the small saphenous vein (for varicosities in the posterior calf) and incompetent perforator veins arising directly from the deep venous system. Correction of reflux is performed at the same time as excision of the symptomatic varicose veins. When superficial venous reflux is present, concomitant reflux in the deep

venous system is often secondary to volume overload, which will resolve with correction of the superficial reflux.

Prognosis

Surgical treatment of superficial vein reflux and excision of varicose veins provide excellent results. The 5-year success rate (as defined as lack of pain and recurrent varicosities) is 85–90%. Simple excision (phlebectomy) or injection sclerotherapy without correction of reflux is associated with recurrence rates over 50%. Even after adequate treatment, secondary tissue changes may persist.

When to Refer

- Absolute indications for referral for saphenous ablation include thrombophlebitis and bleeding.
- Pain and cosmetic concerns are responsible for the majority of referrals for ablation.

Kabnick LS et al. Classification and treatment of endothermal heat-induced thrombosis: recommendations from the American Venous Forum and the Society for Vascular Surgery. J Vasc Surg Venous Lymphat Disord. 2021;9:6. [PMID: 33012690]

DePopas E et al. Varicose veins and lower extremity venous insufficiency. Semin Intervent Radiol. 2018;35:56. [PMID: 29628617]

SUPERFICIAL VENOUS THROMBOPHLEBITIS

ESSENTIALS OF DIAGNOSIS

- Red, painful induration along a superficial vein, usually at the site of a recent intravenous line.
- Marked swelling of the extremity may not occur.

General Considerations

Short-term venous catheterization of superficial arm veins as well as the use of longer-term peripherally inserted central catheter (PICC) lines are the most common cause of superficial thrombophlebitis. Intravenous catheter sites should be observed daily for signs of local inflammation and should be removed if a local reaction develops in the vein. Serious thrombotic or septic complications can occur if this policy is not followed; *S aureus* is the most common pathogen. Other organisms, including fungi, may also be responsible.

Superficial thrombophlebitis may occur spontaneously, often in pregnant or postpartum women or in individuals with varicose veins, or it may be associated with trauma, as with a blow to the leg or following intravenous therapy with irritating solutions. It also may be a manifestation of systemic hypercoagulability secondary to abdominal cancer such as carcinoma of the pancreas and may be the earliest sign of these conditions. Superficial thrombophlebitis related to a PICC may be associated with occult DVT in about 20% of cases, but occult DVT is much less commonly associated with spontaneous superficial thrombophlebitis of the saphenous vein (about 5% of cases). Pulmonary emboli are exceedingly rare and occur from an associated DVT (see Chapters 9 and 14).

Clinical Findings

A. Symptoms and Signs

In spontaneous superficial thrombophlebitis, the great saphenous vein is most often involved. The patient usually experiences a dull pain in the region of the involved vein. Local findings consist of induration, redness, and tenderness along the course of a vein. The process may be localized, or it may involve most of the great saphenous vein and its tributaries. The inflammatory reaction generally subsides in 1–2 weeks; a firm cord may remain for a much longer period. Edema of the extremity is uncommon.

Localized redness and induration at the site of a recent intravenous line requires urgent attention. Proximal extension of the induration and pain with chills and high fever suggest septic phlebitis and requires urgent treatment.

B. Imaging

Duplex ultrasound of the involved extremity is the standard of care to establish the extent of superficial thrombophlebitis and detect the presence of DVT.

Differential Diagnosis

The linear rather than circular nature of the lesion and the distribution along the course of a superficial vein serve to differentiate superficial phlebitis from cellulitis, erythema nodosum, erythema induratum, panniculitis, and fibrositis. Lymphangitis and deep thrombophlebitis must also be considered.

Treatment

For focal, spontaneous thrombophlebitis not near the saphenofemoral junction, local heat and NSAIDs are usually effective in limiting the process. Prophylactic dose fondaparinux or rivaroxaban is recommended for 5 cm or longer superficial thrombophlebitis of the saphenous veins (Table 14–14) and full anticoagulation is reserved for disease that is rapidly progressing or if there is concern for extension into the deep system (Table 14–16). Active malignancy, a history of venous thromboembolism, and known thrombophilia are also indications for full dose anticoagulation. The usual course of treatment of superficial thrombophlebitis is 6 weeks. When the lower extremity superficial thrombosis is less than 5 cm but the patient has risk factors such as hospitalization, immobilization, or recent surgery, prophylactic dose anticoagulation may be deferred unless there is extension of the thrombus on repeat ultrasonography 7–10 days later. If the induration is extensive or is progressing toward the saphenofemoral junction (leg) or cephalo-axillary junction (arm) despite anticoagulation, ligation and division of the vein at the junction of the deep and superficial veins is indicated.

Septic superficial thrombophlebitis is an intravascular abscess and requires urgent treatment with heparin or

fondaparinux (see Table 14–16) to limit further thrombus formation and removal of the offending catheter in catheter-related infections (see Chapter 30). Treat with antibiotics (eg, vancomycin, 15 mg/kg intravenously every 12 hours, plus ceftriaxone, 1 g intravenously every 24 hours). If cultures are positive, therapy should be continued for 7–10 days or for 4–6 weeks if complicating endocarditis cannot be excluded. Surgical excision of the involved vein may also be necessary to control the infection.

Prognosis

With spontaneous thrombophlebitis, the course is generally benign and brief. In patients with phlebitis secondary to varicose veins, recurrent episodes are likely unless correction of the underlying venous reflux and excision of varicosities is done. In contrast, the mortality from septic thrombophlebitis is 20% or higher and requires aggressive treatment. However, if the involvement is localized, the mortality is low and prognosis is excellent with early treatment.

Duffett L et al. Treatment of superficial vein thrombosis: a systematic review and meta-analysis. Thromb Haemost. 2019;119:479. [PMID: 30716777]

CHRONIC VENOUS INSUFFICIENCY

ESSENTIALS OF DIAGNOSIS

- History of prior DVT or leg injury.
- Edema, (brawny) skin hyperpigmentation, subcutaneous lipodermosclerosis in the lower leg.
- Venous ulcers: large ulcerations at or above the medial ankle.

General Considerations

Chronic venous insufficiency is a severe manifestation of venous hypertension. One of the most common etiologies is prior deep venous thrombophlebitis, although about 25% of patients do not have a known history of DVT. In these cases, there may be a history of leg trauma or surgery; obesity is often a complicating factor. Progressive superficial venous reflux is also a common cause. Other causes include congenital or neoplastic obstruction of the pelvic veins or a congenital or acquired arteriovenous fistula.

The basic pathology is caused by valve leaflets that do not coapt because they are either thickened and scarred (post-thrombotic syndrome) or in a dilated vein and are therefore functionally inadequate. With the valves unable to stop venous blood from returning to the foot (venous reflux), the leg develops venous hypertension and an abnormally high hydrostatic force is transmitted to the subcutaneous veins and tissues of the lower leg. The resulting edema results in dramatic and deleterious secondary changes. The stigmata of chronic venous insufficiency include fibrosis of the subcutaneous tissue and skin, pigmentation of skin (hemosiderin taken up by the dermal macrophages) and, later, ulceration, which is extremely slow to heal. Itching may precipitate the formation of ulceration or local wound cellulitis. Dilation of the superficial veins may occur, leading to varicosities. Although surgical treatment for venous reflux can improve symptoms, controlling edema and the secondary skin changes usually require lifelong compression therapy.

Clinical Findings

A. Symptoms and Signs

Progressive pitting edema of the leg (particularly the lower leg) is the primary presenting symptom. Secondary changes in the skin and subcutaneous tissues develop over time (Figure 12–2). The usual symptoms are itching, a dull discomfort made worse by periods of standing, and pain if an ulceration is present. The skin at the ankle is usually taut from swelling, shiny, and a brownish pigmentation (hemosiderin) often develops. If the condition is longstanding, the subcutaneous tissues become thick and fibrous. Ulcerations may occur, usually just above the ankle, on the medial or anterior aspect of the leg. Healing results in a thin scar on a fibrotic base that often breaks down with minor trauma or further bouts of leg swelling. Varicosities may appear (Figure 12–3) that are associated with incompetent perforating veins. Cellulitis, which is often difficult to distinguish from the hemosiderin pigmentation, may be diagnosed by blanching erythema with pain.

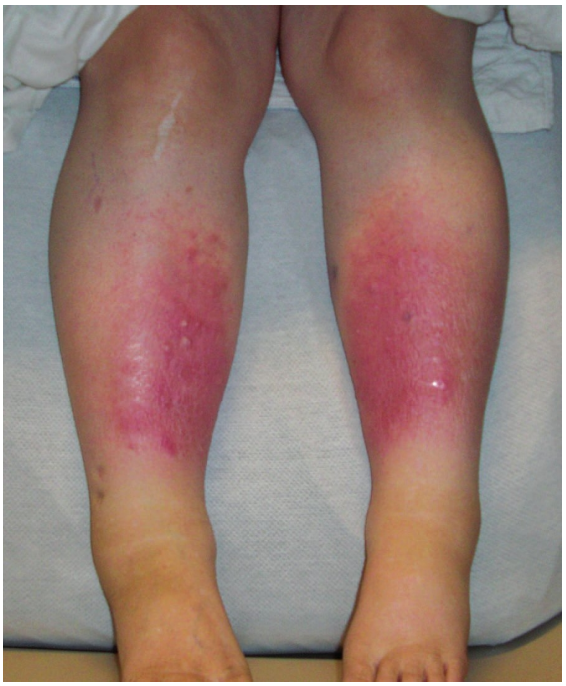
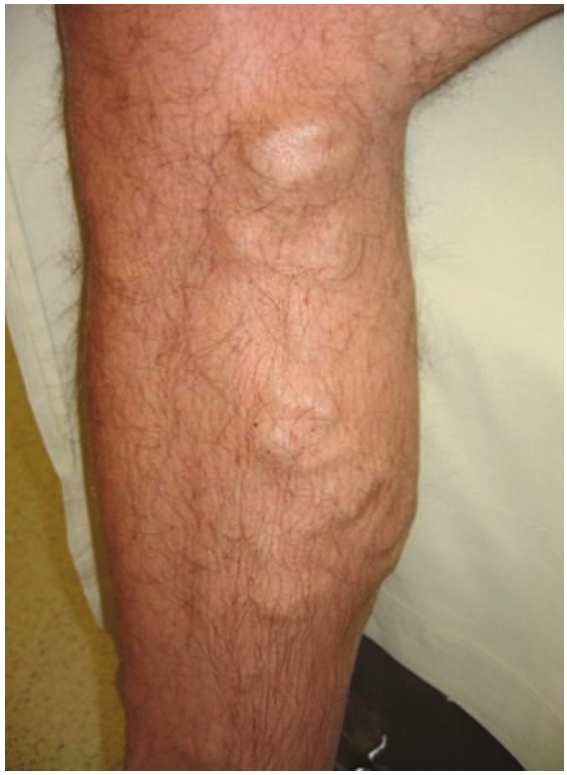


Figure 12–2. Bilateral pretibial edema and erythema consistent with stasis dermatitis (sometimes mimicking cellulitis) in chronic venous insufficiency. (Used, with permission, from Dean SM, Satiani B, Abraham WT. *Color Atlas and Synopsis of Vascular Diseases.* McGraw-Hill, 2014.)



▲ **Figure 12–3.** Varicose veins, manifested as blue, subcutaneous, tortuous veins more than 3 mm in diameter. (Used, with permission, from Dean SM, Satiani B, Abraham WT. *Color Atlas and Synopsis of Vascular Diseases.* McGraw-Hill, 2014.)

B. Imaging

Patients with post-thrombotic syndrome or signs of chronic venous insufficiency should undergo duplex ultrasonography to determine whether superficial reflux is present and to evaluate the degree of deep reflux and obstruction.

Differential Diagnosis

Patients with heart failure, CKD, or decompensated liver disease may have bilateral edema of the lower extremities. Many medications can cause edema (eg, calcium channel blockers, NSAIDs, thiazolidinediones). Swelling from lymphedema involves the feet and may be unilateral, but varicosities are absent. Edema from these causes pits easily and brawny discoloration is rare. Lipedema is a disorder of adipose tissue that occurs almost exclusively in women, is bilateral and symmetric, and is characterized by stopping at a distinct line just above the ankles.

Primary varicose veins may be difficult to differentiate from the secondary varicosities of post-thrombotic syndrome or venous obstruction.

Other conditions associated with chronic ulcers of the leg include neuropathic ulcers from diabetes mellitus, arterial insufficiency (often manifests as painful lateral ankle ulcers with absent pulses; conversely, medial ankle ulcers, are usually due to venous insufficiency), autoimmune diseases (eg, Felty syndrome), sickle cell anemia, erythema induratum (bilateral and usually on the posterior aspect of the lower part of the leg), and fungal infections.

Prevention

Irreversible tissue changes and associated complications in the lower legs can be reduced through early and aggressive anticoagulation of acute DVT to minimize the valve damages and by prescribing compression stockings if chronic edema develops after the DVT has resolved. Treatment of acute iliofemoral DVT with catheter-directed thrombolysis or mechanical thrombectomy does not reduce post-thrombotic syndrome and chronic venous insufficiency.

Treatment

A. General Measures

Fitted, graduated compression stockings (20–30 mm Hg pressure or higher) worn from the foot to just below the knee during the day and evening are the mainstays of treatment and are usually sufficient. When they are not, additional measures, such as avoidance of long periods of sitting or standing, intermittent elevations of the involved leg, and sleeping with the legs kept above the level of the heart, may be necessary to control the swelling. Pneumatic compression of the leg, which can pump the fluid out of the leg, is used in refractory cases.

B. Ulceration

As the primary pathology is edema and venous hypertension, healing of the ulcer will not occur until the edema is controlled and compression is applied. Circumferential nonelastic bandages on the lower leg enhance the pumping action of the calf muscles on venous blood flow out of the calf. A lesion can often be treated on an ambulatory basis by means of a semi-rigid gauze boot made with Unna paste (Gelocast, Medicopaste) or a multi-layer compression dressing (eg, Profore). Initially, the ulcer needs to be debrided and the boot changed every 2–3 days to control ulcer drainage. As the edema and drainage subside, the boot is changed every 5–7 days until the ulcer heals. The ulcer, tendons, and bony prominences must be adequately padded. Alternatively, knee-high graduated compression stockings with an absorbent dressing may be used, if wound drainage is minimal. Home compression therapy with a pneumatic compression device is used in refractory cases, but many patients have severe pain with the "milking" action of the pump device. Some patients will require hospital admission for complete bed rest and leg elevation to achieve ulcer healing. After the ulcer has healed, daily graduated compression stocking therapy is mandatory to prevent ulcer recurrence.

C. Vein Treatment (Reflux or Obstruction)

Treatment of superficial vein reflux (see Varicose Veins, above) has been shown to decrease the recurrence rate of venous ulcers. Where there is substantial obstruction of the femoral or popliteal deep venous system, superficial

varicosities supply the venous return and should not be removed.

Venous stents as treatment of chronic iliac deep vein stenosis or obstruction may improve venous ulcer healing and reduce the ulcer recurrence rate in severe cases.

Prognosis

Edema often recurs, particularly if support stockings that have at least 20–30 mm Hg compression are not worn consistently.

When to Refer

- Patients with significant saphenous reflux should be evaluated for ablation.
- Patients with ulcers should be monitored by an interdisciplinary wound care team so that these challenging wounds receive aggressive care.

Raffetto JD et al. Why venous leg ulcers have difficulty healing: overview on pathophysiology, clinical consequences, and treatment. J Clin Med. 2020;10:29. [PMID: 33374372]

SUPERIOR VENA CAVAL OBSTRUCTION

ESSENTIALS OF DIAGNOSIS

- Swelling of the neck, face, and upper extremities.
- Dilated veins over the upper chest and neck.

General Considerations

Partial or complete obstruction of the superior vena cava is a relatively rare condition that is usually secondary to neoplastic or inflammatory processes in the superior mediastinum. The most frequent causes are (1) neoplasms, such as carcinoma of the lung with direct extension (over 80%), lymphomas, or primary malignant mediastinal tumors; (2) chronic fibrotic mediastinitis, either of unknown origin or secondary to tuberculosis, histoplasmosis, pyogenic infections, or drugs (especially methysergide); (3) DVT, often by extension of the process from the axillary or subclavian vein into the innominate vein and vena cava associated with catheterization of these veins for dialysis or for hyperalimentation; (4) aneurysm of the aortic arch; and (5) constrictive pericarditis.

Clinical Findings

A. Symptoms and Signs

The onset of symptoms is acute or subacute. Symptoms include swelling of the neck and face and upper extremities. Symptoms are often perceived as congestion and present as headache, dizziness, visual disturbances, stupor, syncope, or cough. There is progressive obstruction of the venous drainage of the head, neck, and upper extremities. The cutaneous veins of the upper chest and lower neck become dilated, and flushing of the face and neck develops. Brawny edema of the face, neck, and arms occurs later, and cyanosis of these areas then appears. Cerebral and laryngeal edema ultimately result in impaired function of the brain as well as respiratory insufficiency. Bending over or lying down accentuates the symptoms; sitting quietly is generally preferred. The manifestations are more severe if the obstruction develops rapidly and if the azygos junction or the vena cava between that vein and the heart is obstructed.

B. Laboratory Findings

The venous pressure is elevated (often more than 20 cm of water) in the arm and is normal in the leg. Since lung cancer is a common cause, bronchoscopy is often performed; transbronchial biopsy, however, is relatively contraindicated because of venous hypertension and the risk of bleeding.

C. Imaging

Chest radiographs and a CT scan can define the location and often the nature of the obstructive process, and contrast venography or magnetic resonance venography (MRV) will map out the extent and degree of the venous obstruction and the collateral circulation. Brachial venography or radionuclide scanning following intravenous injection of technetium (Tc-99m) pertechnetate demonstrates a block to the flow of contrast material into the right heart and enlarged collateral veins. These techniques also allow estimation of blood flow around the occlusion as well as serial evaluation of the response to therapy.

Treatment

Conservative measures, such as elevation of the head of the bed and lifestyle modification to avoid bending over, are useful. Balloon angioplasty of the obstructed caval segment combined with stent placement provides prompt relief of symptoms and is the procedure of choice for all etiologies. Occasionally, anticoagulation is needed, while thrombolysis is rarely needed.

Urgent treatment for neoplasm consists of (1) cautious use of intravenous diuretics and (2) mediastinal irradiation, starting within 24 hours, with a treatment plan designed to give a high daily dose of radiation but a short total course of therapy to rapidly shrink the local tumor. Intensive radiation therapy combined with chemotherapy will palliate the process in up to 90% of patients. In patients with a subacute presentation, radiation therapy alone usually suffices. Chemotherapy is added if lymphoma or small-cell carcinoma is diagnosed.

Long-term outcome is complicated by risk of re-occlusion from either thrombosis or neoplasm growth. Surgical procedures to bypass the obstruction are complicated by bleeding from high venous pressure. In cases where the thrombosis is secondary to an indwelling catheter, thrombolysis may be attempted. Clinical judgment is required since a long-standing clot may be fibrotic and the risk of bleeding can outweigh the potential benefit.

Prognosis

The prognosis depends on the nature and degree of obstruction and its speed of onset. Slowly developing forms secondary to fibrosis may be tolerated for years. A high degree of obstruction of rapid onset secondary to cancer is often fatal in a few days or weeks because of increased intracranial pressure and cerebral hemorrhage, but treatment of the tumor with radiation and chemotherapeutic drugs may result in significant palliation. Balloon angioplasty and stenting provide good relief but may require re-treatment for recurrent symptoms due to thrombosis or restenosis.

When to Refer

- Any patient with progressive head and neck swelling should be referred to rule out superior vena cava syndrome.

When to Admit

- Any patient with acute edema of the head and neck or with signs and symptoms of airway compromise, such as hoarseness or stridor, should be admitted.

Azizi AH et al. Superior vena cava syndrome. JACC Cardiovasc Interv. 2020;13:2896. [PMID: 33357528]

DISEASES OF THE LYMPHATIC CHANNELS

LYMPHANGITIS & LYMPHADENITIS

ESSENTIALS OF DIAGNOSIS

- Red streak from wound or cellulitis toward regional lymph nodes, which are usually enlarged and tender.
- Chills, fever, and malaise may be present.

General Considerations

Lymphangitis and lymphadenitis are common manifestations of a bacterial infection that is usually caused by hemolytic streptococci or *S aureus* (or by both organisms) and becomes invasive, generally from an infected wound, cellulitis, or an abscess. The wound may be very small or superficial, or an established abscess may be present, feeding bacteria into the lymphatics. The involvement of the lymphatics is often manifested by a red streak in the skin extending in the direction of the regional lymph nodes.

Clinical Findings

A. Symptoms and Signs

Throbbing pain is usually present at the site of bacterial invasion from a wound, cellulitis, or abscess. Malaise, anorexia, sweating, chills, and fever of 38–40°C develop quickly, often with a rapid pulse. The red streak, when present, may be definite or may be faint and easily missed, especially in dark-skinned patients. The involved regional lymph nodes may be significantly enlarged and are usually quite tender. The infection may progress rapidly, often in a matter of hours, and may lead to septicemia and death.

B. Laboratory Findings

Leukocytosis with a left shift is usually present. Blood cultures may be positive, most often for staphylococcal or streptococcal species. Culture and sensitivity studies of the wound exudate or pus may be helpful in treatment of the more severe or refractory infections but are often difficult to interpret because of skin contaminants.

Differential Diagnosis

The erythema and induration of superficial thrombophlebitis are localized in and around the thrombosed vein. Venous thrombosis is not associated with lymphadenitis, and an entrance wound with secondary cellulitis is generally absent.

Cat-scratch fever *(Bartonella henselae)* is a cause of lymphadenitis; the nodes, though often very large, are relatively nontender. Exposure to cats is common, but the patient may have forgotten about the scratch.

It is extremely important to differentiate cellulitis from acute streptococcal hemolytic gangrene or a necrotizing soft tissue infection. These are deeper infections that may be extensive and are potentially lethal. Patients are more seriously ill; there may be redness due to leakage of red cells, creating a non-blanching erythema; subcutaneous crepitus, a late finding, may be palpated or auscultated; and subcutaneous air may be present on radiography or CT scan. Immediate surgical consultation is needed for wide debridement of all involved deep tissues if a necrotizing infection is suspected.

Treatment

A. General Measures

Prompt treatment should include heat (hot, moist compresses or heating pad), elevation when feasible, and immobilization of the infected area. Analgesics may be prescribed for pain.

B. Specific Measures

Empiric antibiotic therapy for hemolytic streptococci or *S aureus* (or both organisms) should always be instituted. Cephalosporins or extended-spectrum penicillins are commonly used (eg, cephalexin, 0.5 g orally four times daily for 7–10 days; see Table 30–6). Trimethoprim-sulfamethoxazole (two double-strength tablets orally twice daily for 7–10 days) should be considered when there is concern that the pathogen is MRSA (see Tables 30–4 and 30–6). Vancomycin, 15 mg/kg intravenously every 12 hours, is used for patients with signs of a systemic inflammatory response.

C. Wound Care

Any wound that is the initiating site of lymphangitis should be treated aggressively. Any necrotic tissue must be debrided and loculated pus drained.

Prognosis

With proper therapy including an antibiotic effective against the invading bacteria, control of the infection can usually be achieved in a few days. Delayed or inadequate therapy can lead to overwhelming infection with septicemia.

When to Admit

- Infections causing lymphangitis should be treated in the hospital with intravenous antibiotics.
- Debridement may be required and prompt surgical consultation is prudent.

LYMPHEDEMA

ESSENTIALS OF DIAGNOSIS

- Painless persistent edema of one or both lower extremities, primarily in young women.
- Pitting edema without ulceration, varicosities, or stasis pigmentation.
- Lymphangitis and cellulitis may occur.

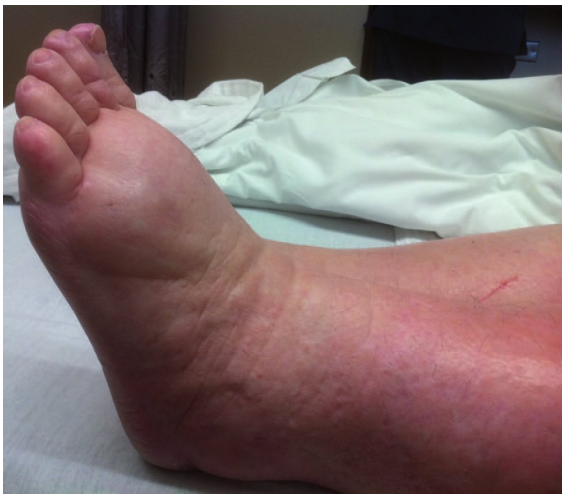
General Considerations

The **primary form** of lymphedema is caused by congenital hypo- or hyperplastic proximal or distal lymphatics. The obstruction may be in the pelvic or lumbar lymph channels and nodes when the disease is extensive and progressive. The **secondary form** of lymphedema involves inflammatory or mechanical lymphatic obstruction from trauma, regional lymph node resection or irradiation, or extensive involvement of regional nodes by malignant disease or filariasis. Lymphedema may occur following surgical removal of the lymph nodes in the groin or axillae. Episodes of acute and chronic inflammation may be superimposed, with further stasis and secondary fibrosis.

Clinical Findings

Hypertrophy of the limb results, with markedly thickened and fibrotic skin and subcutaneous tissue (Figure 12–4) in very advanced cases.

T_2-weighted MRI has been used to identify lymphatics and proximal obstructing masses. Lymphangiography and radioactive isotope studies may identify focal defects in lymph flow but are of little value in planning therapy.



▲ **Figure 12–4. Lymphedema with a dorsal pedal hump and exaggerated skin folds near the ankle.** (Used, with permission, from Dean SM, Satiani B, Abraham WT. *Color Atlas and Synopsis of Vascular Diseases.* McGraw-Hill, 2014.)

Treatment

There is no effective cure for lymphedema; treatment strategies can control the lymphedema and allow normal function. Most patients can be treated with some of the following measures: (1) Aid the flow of lymph out of the extremity through intermittent elevation, especially during the sleeping hours (foot of bed elevated 15–20 degrees, achieved by placing pillows beneath the mattress); constant use of graduated elastic compression stockings; and massage toward the trunk—either by hand or by means of pneumatic pressure devices designed to milk edema out of an extremity. Wound care centers specializing in the care of patients with lymphedema may be helpful. (2) Avoid secondary by means of good hygiene and treatment of any trichophytosis of the toes. Once an infection starts, it should be treated by periods of elevation and antibiotic therapy that covers *Staphylococcus* and *Streptococcus* organisms (see Table 30–6). Infections can be a serious and recurring problem and are often difficult to control. Prophylactic antibiotics have not been shown to be of benefit. (3) Intermittent courses of diuretic therapy, especially in those with premenstrual or seasonal exacerbations, are rarely helpful. (4) Amputation is used only for the rare complication of lymphangiosarcoma in the extremity.

Prognosis

With aggressive treatment, including pneumatic compression devices, good relief of symptoms can be achieved. The long-term outlook is dictated by the associated conditions and avoidance of recurrent cellulitis.

Chen K et al. Surgical management of postmastectomy lymphedema and review of the literature. Ann Plast Surg. 2021;86:S173. [PMID: 33346539]

SHOCK

ESSENTIALS OF DIAGNOSIS

- Hypotension, tachycardia, oliguria, altered mental status.
- Peripheral hypoperfusion and impaired oxygen delivery.
- Four classifications: hypovolemic, cardiogenic, obstructive, or distributive.

General Considerations

Shock occurs when the rate of arterial blood flow is inadequate to meet tissue metabolic needs. This results in regional hypoxia and subsequent lactic acidosis from anaerobic metabolism in peripheral tissues as well as eventual end-organ damage and failure.

Classification

Table 12–1 outlines common causes and mechanisms associated with each type of shock.

A. Hypovolemic Shock

Hypovolemic shock results from decreased intravascular volume secondary to loss of blood or fluids and electrolytes. The etiology may be suggested by the clinical setting (eg, trauma) or by signs and symptoms of blood loss (eg, GI bleeding) or dehydration (eg, vomiting or diarrhea). Compensatory vasoconstriction may transiently maintain the blood pressure but unreplaced losses of over 15% of the intravascular volume can result in hypotension and progressive tissue hypoxia.

B. Cardiogenic Shock

Cardiogenic shock results from cardiac failure with the resultant inability of the heart to maintain adequate tissue perfusion. The clinical definition of cardiogenic shock is evidence of tissue hypoxia due to decreased cardiac output (cardiac index less than 2.2 L/minute/m^2) in the presence of adequate intravascular volume. This is most often caused by MI but can also be due to cardiomyopathy, myocardial contusion, valvular incompetence or stenosis, or arrhythmias. See Chapter 10.

C. Obstructive Shock

Pericardial tamponade, tension pneumothorax, and massive PE can cause an acute decrease in cardiac output resulting in shock. These are medical emergencies requiring prompt diagnosis and treatment.

D. Distributive Shock

Distributive or vasodilatory shock has many causes including sepsis, anaphylaxis, traumatic spinal cord injury, or acute adrenal insufficiency. The reduction in systemic vascular resistance results in inadequate cardiac output and tissue hypoperfusion despite normal circulatory volume.

Table 12–1. Classification of shock by mechanism and common causes.

Hypovolemic shock
Blood loss
Traumatic hemorrhage
Exsanguination
Hemothorax
Hemoperitoneum
Fracture (femur and pelvis)
Nontraumatic hemorrhage
GI bleed
AAA rupture
Ectopic pregnancy rupture
Volume loss
Burns
Skin integrity loss (toxic epidermal necrolysis)
Vomiting
Diarrhea
Hyperosmolar states (eg, hyperosmolar hyperglycemic state)
Third spacing (eg, ascites, pancreatitis)
Decreased intake
Cardiogenic shock
Dysrhythmia
Bradycardias and blocks
Tachycardias
Myocardial disease
Left or right ventricular infarction
Dilated cardiomyopathy
Mechanical
Valvular
Aortic regurgitation from dissection
Papillary muscle rupture from ischemia
Acute valvular rupture from abscess
Ventricular aneurysm rupture
Ventricular septum rupture
Ventricular free wall rupture
Obstructive shock
Tension pneumothorax
Pericardial disease
Pericardial tamponade
Constrictive pericarditis
High-risk (massive) PE
Severe pulmonary hypertension
Auto PEEP from mechanical ventilation
Distributive (vasodilatory) shock
Anaphylactic shock
Septic shock
Neurogenic shock
Drug-induced vasodilation
Adrenal insufficiency

Reproduced with permission from Stone CK, Humphries RL (editors). *Current Emergency Diagnosis & Treatment,* 7th ed. NY: McGraw-Hill, 2011.
PEEP, positive end expiratory pressure.

1. Septic shock—Sepsis is the most common cause of distributive shock and carries a mortality rate of 20–50%. The Society of Critical Care Medicine and the European Society of Intensive Care Medicine's 2016 definition for **sepsis** is life-threatening organ dysfunction caused by a

dysregulated host response to infection from any organism (bacterial, viral, or fungal). **Septic shock** is clinically defined as sepsis with fluid-unresponsive hypotension (systolic blood pressure less than 100 mm Hg), serum lactate level higher than 2 mmol/L, and a need for vasopressors to keep mean arterial pressure (MAP) above 65 mm Hg. The most common cause of septic shock in hospitalized patients is infection with gram-positive or gram-negative organisms, with a growing incidence of infection from multidrug-resistant organisms. Sepsis from viral and fungal organisms is increasing but remain less than that for bacterial infections. Risk factors for septic shock include bacteremia, extremes of age, diabetes mellitus, cancer, immunosuppression, and history of a recent invasive procedure.

Clinical tools to identify sepsis and septic shock—Multiple tools exist to screen for sepsis. The Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS-3) recommend using the Sequential Organ Failure Assessment (SOFA) score to define sepsis (https://en.wikipedia.org/wiki/SOFA_score); an increase of 2 or more SOFA score points in a patient with infection is diagnostic of sepsis with a predicted 10% mortality.

Systemic inflammatory response syndrome (SIRS) criteria is another screening tool. SIRS is defined as a systemic response to a nonspecific infectious or noninfectious insult resulting in at least two of the following findings: (1) body temperature higher than 38°C (100.4°F) or lower than 36°C (96.8°F), (2) heart rate faster than 90 beats per minute, (3) respiratory rate more than 20 breaths per minute or hyperventilation with an arterial carbon dioxide tension ($PaCO_2$) less than 32 mm Hg, or (4) abnormal WBC count (greater than 12,000/mcL or less than 4000/mcL or greater than 10% immature [band] forms). Vasodilatory shock from SIRS is often due to burns; pancreatitis; autoimmune disorders, such as vasculitis or inflammatory colitis; air or amniotic fluid embolus; ischemia; or trauma. The SEPSIS-3 group also introduced the quick SOFA (qSOFA) scoring system, but the poor sensitivity of this measurement led the Surviving Sepsis Campaign Guidelines 2021 to strongly recommend against its use as a single screening tool. Regardless of the screening tools used, performance improvement programs for sepsis screening and standardized treatment procedures are highly encouraged.

2. Neurogenic shock—Neurogenic shock is caused by traumatic spinal cord injury or effects of an epidural or spinal anesthetic. This results in loss of sympathetic tone with a reduction in systemic vascular resistance and hypotension without a compensatory tachycardia. Reflex vagal parasympathetic stimulation evoked by pain, gastric dilation, or fright may simulate neurogenic shock, producing hypotension, bradycardia, and syncope.

3. Endocrine shock—Endocrine shock can arise from hyper- or hypothyroidism or adrenal insufficiency (either primary adrenal crisis from Addison disease or secondary adrenal insufficiency [see Chapter 26]). Adrenal insufficiency most often occurs with abrupt cessation of long-term corticosteroid use, but it can also be precipitated by infection, trauma, surgery, or pituitary injury. In addition to hypotension, symptoms include weakness, nausea, abdominal pain, and confusion. Hypothyroidism can lead to myxedema coma, presenting with vasodilation and depressed cardiac output. Shock from hyperthyroidism most often produces high-output cardiac failure.

Clinical Findings

A. Symptoms and Signs

Hypotension is traditionally defined as a systolic blood pressure of 90 mm Hg or less or a MAP of less than 60–65 mm Hg but must be evaluated relative to the patient's normal blood pressure. A drop in systolic pressure of greater than 10–20 mm Hg or an increase in pulse of more than 15 beats per minute with positional change suggests depleted intravascular volume. However, blood pressure is often not the best indicator of end-organ perfusion because compensatory mechanisms, such as increased heart rate, increased cardiac contractility, and vasoconstriction can occur to prevent hypotension. Patients with hypotension often have cool or mottled extremities and weak or thready peripheral pulses. Splanchnic vasoconstriction may lead to oliguria, bowel ischemia, and liver dysfunction, which can ultimately result in multiorgan failure. Mentation may be normal or patients may become restless, agitated, confused, lethargic, or comatose as a result of inadequate perfusion of the brain.

Hypovolemic shock is evident when signs of hypoperfusion, such as oliguria, altered mental status, and cool extremities, are present. Jugular venous pressure is low, and there is a narrow pulse pressure indicative of reduced stroke volume. Rapid replacement of fluids can restore tissue perfusion. In **cardiogenic shock,** there are also signs of global hypoperfusion with oliguria, altered mental status, and cool extremities. Jugular venous pressure is elevated and there may be evidence of pulmonary edema with respiratory compromise in the setting of left-sided heart failure. *A transthoracic echocardiogram (TTE) or a transesophageal echocardiogram (TEE) is an effective diagnostic tool to differentiate hypovolemic from cardiogenic shock.* In hypovolemic shock, the LV will be small because of decreased filling, but contractility is often preserved. In cardiogenic shock, there is a decrease in LV contractility. The LV may appear dilated and full because of the inability of the LV to eject a sufficient stroke volume.

In **obstructive shock**, the central venous pressure may be elevated but the TTE or TEE may show reduced LV filling, a pericardial effusion in the case of tamponade, thickened pericardium in the case of pericarditis, or right ventricular dysfunction in the case of massive PE. Pericardiocentesis or pericardial window for pericardial tamponade, chest tube placement for tension pneumothorax, or catheter-directed thrombolytic therapy for massive PE can be life saving in cases of obstructive shock.

In **distributive shock,** signs include hyperdynamic heart sounds, warm extremities initially, and a wide pulse pressure indicative of large stroke volume. The echocardiogram may show a hyperdynamic LV. **Septic shock** is diagnosed when there is clinical evidence of infection in the

setting of persistent hypotension and evidence of organ hypoperfusion, such as lactic acidosis, decreased urinary output, or altered mental status despite adequate volume resuscitation (see Clinical Tools to Identify Sepsis and Septic Shock, above). **Neurogenic shock** is diagnosed when there is evidence of CNS injury and persistent hypotension despite adequate volume resuscitation. A history of long-term corticosteroid use or thyroid disease can increase the likelihood of **endocrine shock.**

B. Laboratory Findings and Imaging

Blood tests should include CBC, electrolytes, glucose, arterial blood gas determinations, coagulation parameters, lactate levels, typing and cross-matching, and bacterial cultures. An ECG and chest radiograph should be part of the initial assessment. Point-of-care ultrasonography can rapidly assess global cardiac function, presence of pericardial effusion, and intravascular volume status via inferior vena cava inspection in cases of undifferentiated hypotension. A TTE can more formally assess right- and left-sided filling pressures and cardiac output.

Treatment

A. General Measures

Treatment depends on prompt diagnosis and an accurate appraisal of inciting conditions. Initial management consists of basic life support with an assessment of the patient's circulation, airway, and breathing. This may entail airway intubation and mechanical ventilation. Ventilatory failure should be anticipated in patients with severe metabolic acidosis due to shock. Mechanical ventilation along with sedation can decrease respiratory muscle oxygen demand and allow improved oxygen delivery to hypoperfused tissues. Intravenous access and fluid resuscitation should be instituted along with cardiac monitoring and assessment of hemodynamic parameters such as blood pressure and heart rate. Cardiac monitoring can detect myocardial ischemia or malignant arrhythmias, which can be treated by standard advanced cardiac life support (ACLS) protocols.

Unresponsive or minimally responsive patients should have their glucose checked immediately, and if their glucose levels are low, 1 ampule of 50% dextrose intravenously should be given. An arterial line should be placed for continuous blood pressure measurement, and an indwelling urinary catheter should be inserted to monitor urinary output.

B. Hemodynamic Measurements

Early consideration is given to placement of a central venous catheter (CVC) (also known as a central line) for infusion of fluids and medications and for hemodynamic pressure measurements. A CVC can provide measurements of the central venous pressure (CVP) and the central venous oxygen saturation ($ScvO_2$), both of which can be used to manage septic and cardiogenic shock. Pulmonary artery catheters (PACs) allow measurement of the pulmonary artery pressure, left-sided filling pressure or the pulmonary capillary wedge pressure (PCWP), the mixed venous oxygen saturation (SvO_2), and cardiac output. Multiple studies suggest that PACs do not increase overall mortality or length of hospital stay but are associated with higher use of inotropes and intravenous vasodilators in select groups of critically ill patients. The attendant risks associated with PACs (infection, arrhythmias, vein thrombosis, and pulmonary artery rupture) can be as high as 4–9%; thus, the routine use of PACs cannot be recommended. However, in complex situations, PACs may be useful in distinguishing between cardiogenic and septic shock, so the value of the information they might provide must be carefully weighed in each patient. TTE is a noninvasive alternative to the PAC. TTE can provide information about the pulmonary artery pressure and current cardiac function, including cardiac output. The $ScvO_2$, which is obtained through the CVC, can be used as a surrogate for the SvO_2, which is obtained through the PAC. Pulse pressure variation, as determined by arterial line waveform analysis, or stroke volume variation is much more sensitive than CVP as dynamic measures of fluid responsiveness in volume resuscitation, but these measurements have only been validated in patients who are mechanically ventilated with tidal volumes of 8 mL/kg, not triggering the ventilator, and in normal sinus rhythm. Point-of-care ultrasound measurements of the inferior vena cava (IVC) can suggest intravascular volume status and guide fluid replacement. If the patient is mechanically ventilated and the IVC dilates ~15–20% with inspiration, they are likely to respond to intravenous fluids. If the patient is spontaneously breathing, they may be fluid-responsive if their IVC is less than 2 cm in diameter and collapses by more than 50% with each inspiration.

A CVP less than 5 mm Hg suggests hypovolemia, and a CVP greater than 18 mm Hg suggests volume overload, cardiac failure, tamponade, or pulmonary hypertension. A cardiac index lower than 2 L/minute/m^2 indicates a need for inotropic support. A cardiac index higher than 4 L/minute/m^2 in a hypotensive patient is consistent with early septic shock. The systemic vascular resistance is low (less than 800 dynes · s/cm^{-5}) in sepsis and neurogenic shock and high (greater than 1500 dynes · s/cm^{-5}) in hypovolemic and cardiogenic shock. Treatment is directed at maintaining a CVP of 8–12 mm Hg, a MAP of 65 mm Hg or higher, a cardiac index of 2–4 L/minute/m^2, and a $ScvO_2$ greater than 70%.

C. Volume Replacement

Volume replacement is critical in the initial management of shock. **Hemorrhagic shock** is treated with immediate efforts to achieve hemostasis and rapid infusions of blood substitutes, such as type-specific or type O negative packed RBCs or whole blood, which provides extra volume and clotting factors. Each unit of PRBC or whole blood is expected to raise the hematocrit by 3%. **Hypovolemic shock** secondary to dehydration is managed with rapid boluses of isotonic crystalloid solutions, usually in 1-L increments. **Cardiogenic shock** in the absence of fluid overload requires smaller boluses of crystalloid fluid challenges, usually in increments of 250 mL. **Septic shock** usually requires large volumes of fluid for resuscitation (typically 30 mL/kg) as the associated capillary leak releases

fluid into the extravascular space. *Caution must be used in cases of large-volume resuscitation with unwarmed fluids because this can produce hypothermia, which can lead to hypothermia-induced coagulopathy.* Warming of fluids before administration can avoid this complication.

Choice of resuscitation fluid—Crystalloid solution is the resuscitation fluid of choice in most settings. Historically, 0.9% saline was the most widely used crystalloid solution in resuscitation. Data suggest that balanced crystalloids, like lactated Ringer solution or Plasma-Lyte, are associated with less kidney injury, fewer instances of hyperchloremic metabolic acidosis, and decreased overall mortality. Comparisons of 0.9% saline and colloid (albumin) solutions in critically ill patients found no difference in outcome except in patients with traumatic brain injury, where albumin resuscitation led to higher mortality. Thus, the use of balanced crystalloid solutions for volume resuscitation in shock is favored. If the patient does not respond to fluid resuscitation, early use of vasopressors should be considered.

D. Early Goal-Directed Therapy

Compensated shock can occur in the setting of normalized hemodynamic parameters with ongoing global tissue hypoxia. Traditional endpoints of resuscitation such as blood pressure, heart rate, urinary output, mental status, and skin perfusion can therefore be misleading. Following set protocols for the treatment of septic shock by adjusting the use of fluids, vasopressors, and inotropes to meet hemodynamic targets (MAP 65 mm Hg or higher, CVP 8–12 mm Hg, $ScvO_2$ greater than 70%) is termed **early goal-directed therapy (EGDT).** Lactate clearance (a decline of lactate levels) of more than 10% can be used as a substitute for $ScvO_2$ criteria if $ScvO_2$ monitoring is not available.

The 2021 Surviving Sepsis Campaign's recommendations for patients with sepsis or septic shock are to measure lactate level; obtain blood cultures prior to administration of broad-spectrum antibiotics, *which should occur within 1 hour of sepsis diagnosis;* and administer 30 mL/kg balanced crystalloid (lactated Ringer solution or Plasma-Lyte) for hypotension or lactate greater than 4 mmol/L within the first 3 hours of presentation. Smaller resuscitation volumes may be appropriate for patients with heart failure, cirrhosis, or advanced kidney disease. Vasopressors should be administered for hypotension not responsive to initial fluid resuscitation to maintain MAP 65 mm Hg or higher. Remeasure lactate if initial level was high, and reassess volume status and tissue perfusion frequently. A meta-analysis of hemodynamic optimization trials suggests that early treatment before the development of organ failure results in improved survival, and patients who respond well to initial efforts demonstrate a survival advantage over nonresponders.

E. Medications

1. Vasoactive therapy—Vasopressors and inotropic agents are administered only after adequate fluid resuscitation. Choice of vasoactive therapy depends on the presumed etiology of shock as well as cardiac output. If there is continued hypotension with evidence of high cardiac output after adequate volume resuscitation (as in septic shock), then vasopressor support is needed to improve vasomotor tone. If there is evidence of low cardiac output with high filling pressures, inotropic support is needed to improve contractility.

a. Distributive (vasodilatory) shock—When increased vasoconstriction is required to maintain an adequate perfusion pressure, alpha-adrenergic catecholamine agonists (such as norepinephrine and phenylephrine) are generally used. Although norepinephrine is both an alpha-adrenergic and beta-adrenergic agonist, it preferentially increases MAP over cardiac output. The initial dose is 1–2 mcg/minute as an intravenous infusion, titrated to maintain MAP at 65 mm Hg or higher. The usual maintenance dose is 2–4 mcg/minute intravenously (maximum dose is 30 mcg/minute). Patients with refractory shock may require dosages of 10–30 mcg/minute intravenously. Epinephrine, also with both alpha-adrenergic and beta-adrenergic effects, may be used in severe shock and during acute resuscitation. It is the vasopressor of choice for anaphylactic shock. For severe shock, give epinephrine 1 mcg/minute as a continuous intravenous infusion initially and titrate to hemodynamic response; the usual dosage range is 1–10 mcg/minute intravenously.

Dopamine has variable effects according to dosage. At low doses (2–5 mcg/kg/minute intravenously), stimulation of dopaminergic and beta-adrenergic receptors produces increased glomerular filtration, heart rate, and contractility. At doses of 5–10 mcg/kg/minute, beta-1-adrenergic effects predominate, resulting in an increase in heart rate and cardiac contractility. At higher doses (greater than 10 mcg/kg/minute), alpha-adrenergic effects predominate, resulting in peripheral vasoconstriction. The maximum dose is typically 50 mcg/kg/minute.

There is no evidence documenting a survival benefit from, or the superiority of, a particular vasopressor in septic shock. Norepinephrine is the initial vasopressor of choice in septic shock to maintain the MAP at 65 mm Hg or higher. Phenylephrine can be used for hyperdynamic septic shock if dysrhythmias or tachycardias prevent the use of agents with beta-adrenergic activity. In meta-analyses, the use of dopamine as a first-line vasopressor in septic shock resulted in an *increase* in 28-day mortality and a higher incidence of arrhythmic events. Dopamine should only be used as an alternative to norepinephrine in select patients with septic shock, including patients with significant bradycardia or low potential for tachyarrhythmias.

Vasopressin (ADH) is often used as an *adjunctive therapy* to catecholamine vasopressors in the treatment of distributive shock. Vasopressin causes peripheral vasoconstriction via V1 receptors located on smooth muscle cells. Vasopressin also potentiates the effects of catecholamines on the vasculature and stimulates cortisol production. Intravenous infusion of vasopressin at a low dose (0.01–0.04 units/minute) as a second agent to norepinephrine has been beneficial in septic patients with hypotension refractory to fluid resuscitation and conventional catecholamine vasopressors. Higher doses of vasopressin decrease cardiac output and may put patients at greater risk for splanchnic

and coronary artery ischemia. Studies do not favor the use of vasopressin as first-line therapy.

Angiotensin II, a component of the renin-angiotensin-aldosterone system axis, is a potent direct vasoconstrictor that acts on the arteries and veins to increase blood pressure. Angiotensin II (Giapreza) can be considered as an *additional agent* in vasodilatory shock that is refractory to catecholamines and vasopressin. The recommended starting dose is 20 ng/kg/minute via continuous intravenous infusion through a central venous line. It can be titrated every 5 minutes by increments of up to 15 ng/kg/minute as needed to achieve MAP goals, but not to exceed 80 ng/kg/minute during the first 3 hours of use. Maintenance doses should not exceed 40 ng/kg/minute. Concurrent venous thromboembolism (VTE) prophylaxis is indicated as studies revealed a higher incidence of VTE with angiotensin II use.

B. Cardiogenic shock—Given meta-analyses documenting decreased mortality, expert opinion suggests norepinephrine be the first-line vasopressor for cardiogenic shock. Dobutamine, a predominantly beta-adrenergic agonist, increases contractility and decreases afterload. It is used for patients with low cardiac output and high PCWP but who do not have hypotension. Dobutamine can be added to a vasopressor if there is reduced myocardial function (decreased cardiac output and elevated PCWP), or if there are signs of hypoperfusion despite adequate volume resuscitation and an adequate MAP. The initial dose is 0.1–0.5 mcg/kg/minute intravenous infusion, which can be titrated every few minutes to hemodynamic effect; the usual dosage range is 2–20 mcg/kg/minute intravenously. Tachyphylaxis can occur after 48 hours secondary to the downregulation of beta-adrenergic receptors. Milrinone is a phosphodiesterase inhibitor that can be substituted for dobutamine. A 2021 study of patients with cardiogenic shock found no significant difference in mortality when comparing milrinone to dobutamine. Amrinone is another phosphodiesterase inhibitor that can be used. These phosphodiesterase inhibitor drugs increase cyclic AMP levels and increase cardiac contractility, bypassing the beta-adrenergic receptor. Vasodilation is a side effect of both amrinone and milrinone.

2. Antibiotics—Definitive therapy for septic shock includes early initiation of empiric broad-spectrum antibiotics (see Table 30–5) after appropriate cultures have been obtained and within 1 hour of recognition of septic shock. Imaging studies may prove useful to attempt localization of sources of infection. Surgical management may also be necessary if necrotic tissue or loculated infections are present in attempts to control the source of infection.

3. Corticosteroids—Corticosteroids are the treatment of choice in patients with shock secondary to adrenal insufficiency, defined as a cortisol response of 9 mcg/dL or less after one injection of 250 mcg of corticotropin. Studies supporting corticosteroid use in patients with shock from sepsis or other etiologies are mixed but meta-analyses are slightly in favor of their use. The ADRENAL study demonstrated shorter time to shock resolution (3 days vs 4 days) but no difference in 90-day mortality. The APROCCHSS study demonstrated lower 90-day all-cause mortality for patients receiving hydrocortisone plus fludrocortisone. Notably, some worse outcomes were observed from increased rates of secondary infections. Corticosteroids can be administered in refractory shock to decrease shock duration; the current recommended regimen is hydrocortisone 50 mg intravenously every 6 hours for 5–7 days.

F. Other Treatment Modalities

Cardiac failure may require use of transcutaneous or transvenous pacing or placement of an intra-arterial balloon pump or LV assist device. Emergent revascularization by percutaneous angioplasty or coronary artery bypass surgery appears to improve long-term outcome with increased survival compared with initial medical stabilization for patients with myocardial ischemia leading to cardiogenic shock (see Chapter 10). Urgent renal replacement therapy may be indicated for maintenance of fluid and electrolyte balance during AKI resulting in shock from multiple modalities. Studies do not support the use of intravenous vitamin C as treatment for sepsis.

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13 Blood Disorders

Lloyd E. Damon, MD
Charalambos Babis Andreadis, MD, MSCE

ANEMIAS

General Approach to Anemias

Anemia is present in adults if the hematocrit is below 41% (hemoglobin less than 13.6 g/dL [135 g/L]) in males or below 36% (hemoglobin less than 12 g/dL [120 g/L]) in females. Congenital anemia is suggested by the patient's personal and family history. The most common cause of anemia is iron deficiency. Poor diet may result in folic acid deficiency and contribute to iron deficiency, but bleeding is the most common cause of iron deficiency in adults. Physical examination demonstrates pallor. Attention to physical signs of primary hematologic diseases (lymphadenopathy; hepatosplenomegaly; or bone tenderness, especially in the sternum or anterior tibia) is important. Mucosal changes such as a smooth tongue suggest megaloblastic anemia.

Anemias are classified according to their pathophysiologic basis, ie, whether related to diminished production (relative or absolute reticulocytopenia) or to increased production due to accelerated loss of RBCs (reticulocytosis) (Table 13–1), and according to RBC size (Table 13–2). A reticulocytosis occurs in one of three pathophysiologic states: acute blood loss, recent replacement of a missing erythropoietic nutrient, or reduced RBC survival (ie, hemolysis). A severely microcytic anemia (mean corpuscular volume [MCV] less than 70 fL) is due either to iron deficiency or thalassemia, while a severely macrocytic anemia (MCV greater than 120 fL) is almost always due to either megaloblastic anemia or to cold agglutinins in blood analyzed at room temperature. A bone marrow biopsy is generally needed to complete the evaluation of anemia when the blood laboratory evaluation fails to reveal an etiology, when there are additional cytopenias present, or when an underlying primary or secondary bone marrow process is suspected.

IRON DEFICIENCY ANEMIA

ESSENTIALS OF DIAGNOSIS

- Iron deficiency: serum ferritin is < 12 ng/mL (27 pmol/L) or < 30 ng/mL (67 pmol/L) if also anemic.
- Caused by bleeding unless proved otherwise.
- Responds to iron therapy.

General Considerations

Iron deficiency is the most common cause of anemia worldwide. The causes are listed in Table 13–3. Aside from circulating RBCs, the major location of iron in the body is the storage pool as ferritin or as hemosiderin in macrophages.

The average American diet contains 10–15 mg of iron per day. About 10% of this amount is absorbed in the stomach, duodenum, and upper jejunum under acidic conditions. Dietary iron present as heme is efficiently absorbed (10–20%) but nonheme iron less so (1–5%), largely because of interference by phosphates, tannins, and other food constituents. The major iron transporter from the diet across the intestinal lumen is ferroportin, which also facilitates the transport of iron to apotransferrin in macrophages for delivery to erythroid progenitor cells in the bone marrow prepared to synthesize hemoglobin. Hepcidin, which is increasingly produced during inflammation, negatively regulates iron transport by promoting the degradation of ferroportin. Small amounts of iron—approximately 1 mg/day—are normally lost through exfoliation of skin and GI mucosal cells.

Menstrual blood loss plays a major role in iron metabolism. The average monthly menstrual blood loss is approximately 50 mL but may be five times greater in some individuals. Women with heavy menstrual losses must absorb 3–4 mg of iron from the diet each day to maintain adequate iron stores, which is not commonly achieved. Women with menorrhagia of this degree will almost always become iron deficient without iron supplementation.

In general, iron metabolism is balanced between absorption of 1 mg/day and loss of 1 mg/day. Pregnancy and lactation upset the iron balance since requirements increase to 2–5 mg of iron per day. Normal dietary iron cannot supply these requirements, and medicinal iron is needed during pregnancy and lactation. Decreased iron absorption can also cause iron deficiency, such as in people affected by celiac disease (gluten enteropathy), and it also commonly occurs after gastric resection or jejunal bypass surgery.

Table 13–1. Classification of anemia by RBC pathophysiology.

Decreased RBC production (relative or absolute reticulocytopenia)
Hemoglobin synthesis lesion: iron deficiency, thalassemia, anemia of chronic disease, hypoerythropoietinemia
DNA synthesis lesion: megaloblastic anemia, folic acid deficiency, DNA synthesis inhibitor medications
Hematopoietic stem cell lesion: aplastic anemia, leukemia
Bone marrow infiltration: carcinoma, lymphoma, fibrosis, sarcoidosis, Gaucher disease, others
Immune-mediated inhibition: aplastic anemia, pure RBC aplasia
Increased RBC destruction or accelerated RBC loss (reticulocytosis)
Acute blood loss
Hemolysis (intrinsic)
Membrane lesion: hereditary spherocytosis, elliptocytosis
Hemoglobin lesion: sickle cell, unstable hemoglobin
Glycolysis lesion: pyruvate kinase deficiency
Oxidation lesion: glucose-6-phosphate dehydrogenase deficiency
Hemolysis (extrinsic)
Immune: warm antibody, cold antibody
Microangiopathic: disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, mechanical cardiac valve, paravalvular leak
Infection: *Clostridium perfringens*, malaria
Hypersplenism

The most important cause of iron deficiency anemia in adults is chronic blood loss, especially menstrual and GI blood loss. Iron deficiency demands a search for a source of GI bleeding if other sites of blood loss (excess uterine bleeding, hematuria, and repeated blood donations) are excluded. Prolonged aspirin or NSAID use may cause it without a documented structural lesion. Celiac disease, even when asymptomatic, can cause iron deficiency through poor absorption in the GI tract. Zinc deficiency is another cause of poor iron absorption. Chronic hemoglobinuria may lead to iron deficiency, but this is uncommon. Traumatic hemolysis due to a prosthetic cardiac valve and other causes of intravascular hemolysis (eg, paroxysmal nocturnal hemoglobinuria) should also be considered. The cause of iron deficiency is not found in up to 5% of cases.

Table 13–2. Classification of anemia by mean RBC volume (MCV).

Microcytic
Iron deficiency
Thalassemia
Anemia of chronic disease
Lead toxicity
Zinc deficiency
Macrocytic (Megaloblastic)
Vitamin B_{12} deficiency
Folate deficiency
DNA synthesis inhibitors
Macrocytic (Nonmegaloblastic)
Aplastic anemia
Myelodysplasia
Liver disease
Reticulocytosis
Hypothyroidism
Bone marrow failure state (eg, aplastic anemia, marrow infiltrative disorder, etc)
Copper deficiency
Normocytic
Kidney disease
Non-thyroid endocrine gland failure
Copper deficiency
Mild form of most acquired microcytic or macrocytic etiologies of anemia

Table 13–3. Causes of iron deficiency.

Deficient diet
Decreased absorption
Autoimmune gastritis
Celiac disease
Helicobacter pylori gastritis
Hereditary iron-refractory iron deficiency anemia
Zinc deficiency
Increased requirements
Pregnancy
Lactation
Blood loss (chronic)
GI
Menstrual
Blood donation
Hemoglobinuria
Iron sequestration
Pulmonary hemosiderosis
Idiopathic

Pure iron deficiency might prove refractory to oral iron replacement. Refractoriness is defined as a hemoglobin increment of less than 1 g/dL (10 g/L) after 4–6 weeks of 100 mg/day of elemental oral iron. The differential diagnosis in these cases (Table 13–3) includes malabsorption from autoimmune gastritis, *Helicobacter pylori* gastric infection, celiac disease, and hereditary iron-refractory iron deficiency anemia. Iron-refractory iron deficiency anemia is a rare autosomal recessive disorder due to mutations in the transmembrane serine protease 6 (*TMPRSS6*) gene, which normally downregulates hepcidin. In iron-refractory iron deficiency anemia, hepcidin levels are normal to high and ferritin levels are low-normal despite the iron deficiency.

Clinical Findings

A. Symptoms and Signs

The primary symptoms of iron deficiency anemia are those of the anemia itself (easy fatigability, tachycardia, palpitations, and dyspnea on exertion). Severe deficiency causes skin and mucosal changes, including a smooth tongue, brittle nails, spooning of nails (koilonychia), and cheilosis. Dysphagia due to the formation of esophageal webs (Plummer-Vinson syndrome) may occur in severe iron deficiency. Pica (ie, craving for specific foods [ice chips, etc] not rich in iron) develops in many iron-deficient patients.

B. Laboratory Findings

Iron deficiency develops in stages. The first is depletion of iron stores without anemia followed by anemia with a normal RBC size (normal MCV) followed by anemia with reduced RBC size (low MCV). The reticulocyte count is low or inappropriately normal. Ferritin is a measure of total body iron stores. A ferritin value less than 12 ng/mL (27 pmol/L) (in the absence of scurvy) is a highly reliable indicator of reduced iron stores. Note that the lower limit of normal for ferritin is often below 12 ng/mL (27 pmol/L) in women due to the fact that the normal ferritin range is generated by including healthy menstruating women who are iron deficient but not anemic. However, because serum ferritin levels may rise in response to inflammation or other stimuli, a normal or elevated ferritin level does not exclude a diagnosis of iron deficiency. A ferritin level less than 30 ng/mL (67 pmol/L) almost always indicates iron deficiency in anyone who is anemic. As iron deficiency progresses, serum iron values decline to less than 30 mcg/dL (67 pmol/L) and transferrin (the iron transport protein) levels rise to compensate, leading to transferrin saturations of less than 15%. Low transferrin saturation is also seen in anemia of inflammation, so caution in the interpretation of this test is warranted. Isolated iron deficiency anemia has a low hepcidin level, not yet a clinically available test. As the MCV falls (ie, microcytosis), the blood smear shows hypochromic microcytic cells. With further progression, anisocytosis (variations in RBC size) and poikilocytosis (variation in shape of RBCs) develop. Severe iron deficiency will produce a bizarre peripheral blood smear, with severely hypochromic cells, target cells, and pencil-shaped or cigar-shaped cells. Bone marrow biopsy for evaluation of iron stores is rarely performed. If the biopsy is done, it shows the absence of iron in erythroid progenitor cells by Prussian blue staining. The platelet count is commonly increased, but it usually remains under 800,000/mcL (800×10^9/L).

Differential Diagnosis

Other causes of microcytic anemia include anemia of chronic disease (specifically, anemia of inflammation), thalassemia, lead poisoning, zinc deficiency, and congenital X-linked sideroblastic anemia. Anemia of chronic disease is characterized by normal or increased iron stores in bone marrow macrophages and a normal or elevated ferritin level; the serum iron and transferrin saturation are low, often drastically so, and the total iron-binding capacity (TIBC) (the blood's capacity for iron to bind to transferrin) and transferrin are either normal or low. Thalassemia produces a greater degree of microcytosis for any given level of hemoglobin than does iron deficiency and, unlike virtually every other cause of anemia, has a normal or elevated (rather than a low) RBC count as well as a reticulocytosis. In thalassemia, RBC morphology on the peripheral smear resembles severe iron deficiency.

Treatment

The diagnosis of iron deficiency anemia can be made either by the laboratory demonstration of an iron-deficient state or by evaluating the response to a therapeutic trial of iron replacement. Since the anemia itself is rarely life-threatening, the most important part of management is identification of the cause—especially a source of occult blood loss.

A. Oral Iron

Ferrous sulfate, 325 mg once daily or every other day on an empty stomach, is a standard approach for replenishing iron stores. As oral iron stimulates hepcidin production, once daily or every other day dosing maximizes iron absorption compared to multiple doses per day, and with fewer side effects. Nausea and constipation limit compliance with ferrous sulfate. Extended-release ferrous sulfate with mucoprotease is a well-tolerated oral preparation. Taking ferrous sulfate with food reduces side effects but also its absorption. An appropriate response to oral iron is a return of the hematocrit level halfway toward normal within 3 weeks with full return to baseline after 2 months. Iron therapy should continue for 3–6 months after restoration of normal hematologic values to replenish iron stores. Failure of response to iron therapy is usually due to noncompliance, although occasional patients may absorb iron poorly, particularly if the stomach is achlorhydric. Such patients may benefit from concomitant administration of oral ascorbic acid. Other reasons for failure to respond include incorrect diagnosis (anemia of chronic disease, thalassemia), celiac disease, and ongoing blood loss that exceeds the rate of new erythropoiesis. Treatment of *H pylori* infection, in appropriate cases, can improve oral iron absorption.

B. Parenteral Iron

The indications are intolerance of or refractoriness to oral iron (including those with iron-refractory iron deficiency anemia), GI disease (usually IBD) precluding the use of oral iron, and continued blood loss that cannot be corrected, such as chronic hemodialysis. Historical parenteral iron preparations, such as high-molecular-weight iron dextran, were problematic due to long infusion times (hours), polyarthralgia, and hypersensitivity reactions, including anaphylaxis. Current parenteral iron preparations coat the iron in protective carbohydrate shells or contain low-molecular-weight iron dextran, are safe, and can be administered over 15 minutes to 1 hour. Most iron-deficient patients need 1–1.5 g of parenteral iron; this dose corrects for the iron deficit and replenishes iron stores for the future.

Ferric pyrophosphate citrate (Triferic) is an FDA-approved additive to the dialysate designed to replace the 5–7 mg of iron that patients with CKD tend to lose during each hemodialysis treatment. Ferric pyrophosphate citrate delivers sufficient iron to the marrow to maintain hemoglobin and not increase iron stores; it may obviate the need for intravenous iron in hemodialysis patients.

When to Refer

Patients should be referred to a hematologist if the suspected diagnosis is not confirmed or if they are not responsive to oral iron therapy.

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ANEMIA OF CHRONIC DISEASE

ESSENTIALS OF DIAGNOSIS

- Mild or moderate normocytic or microcytic anemia.
- Normal or increased ferritin and normal or reduced transferrin.
- Underlying chronic disease.

General Considerations

Many chronic systemic diseases are associated with mild or moderate anemia. The anemias of chronic disease are characterized according to etiology and pathophysiology. First, the **anemia of inflammation** is associated with chronic inflammatory states (such as IBD, rheumatologic disorders, chronic infections, and malignancy) and is mediated through hepcidin (a negative regulator of ferroportin) primarily via elevated IL-6, resulting in reduced iron uptake in the gut and reduced iron transfer from macrophages to erythroid progenitor cells in the bone marrow. This is referred to as iron-restricted erythropoiesis since the patient is iron replete. There is also reduced responsiveness to erythropoietin, the elaboration of hemolysins that shorten RBC survival, and the production of other inflammatory cytokines that dampen RBC production. The serum iron is low in the anemia of inflammation. Second, the **anemia of organ failure** can occur with kidney disease, liver failure, and endocrine gland failure. Erythropoietin is reduced and the RBC mass decreases in response to the diminished signal for RBC production; the serum iron is normal (except in CKD where it is low due to the reduced hepcidin clearance and subsequent enhanced degradation of ferroportin). Third, the **anemia of older adults** is present in up to 20% of individuals over age 85 years in whom a thorough evaluation for an explanation of anemia is negative. The anemia is a consequence of (1) a relative resistance to RBC production in response to erythropoietin, (2) a decrease in erythropoietin production relative to the nephron mass, (3) a negative erythropoietic influence of higher levels of chronic inflammatory cytokines in older adults, and (4) the presence of various somatic mutations in myeloid genes typically associated with myeloid neoplasms. The latter condition is now referred to as **clonal cytopenias of undetermined significance,** which has a 15–20% per year rate of transformation to a myeloid neoplasm, such as a myelodysplastic syndrome (MDS). The serum iron is normal.

Clinical Findings

A. Symptoms and Signs

The clinical features are those of the causative condition. The diagnosis should be suspected in patients with known chronic diseases. In cases of significant anemia, coexistent iron deficiency or folic acid deficiency should be suspected. Decreased dietary intake of iron or folic acid is common in chronically ill patients, many of whom will also have ongoing GI blood losses. Patients undergoing hemodialysis regularly lose both iron and folic acid during dialysis.

B. Laboratory Findings

The hematocrit rarely falls below 60% of baseline (except in kidney failure). The MCV is usually normal or slightly reduced. RBC morphology is usually normal, and the reticulocyte count is mildly decreased or normal.

1. Anemia of inflammation—In the anemia of inflammation, serum iron and transferrin values are low, and the transferrin saturation may be extremely low, leading to an erroneous diagnosis of iron deficiency. In contrast to iron deficiency, serum ferritin values should be normal or increased. A serum ferritin value less than 30 ng/mL (67 pmol/L) indicates coexistent iron deficiency. Anemia of inflammation has elevated hepcidin levels; however, no clinical test is yet available. A particular challenge is the diagnosis of iron deficiency in the setting of the anemia of inflammation, in which the serum ferritin can be as high as 200 ng/mL (450 pmol/L). The diagnosis is established by a bone marrow biopsy with iron stain. Absent iron staining indicates iron deficiency, whereas iron localized in marrow macrophages indicates pure anemia of inflammation. However, bone marrow biopsies are rarely done for this purpose. Two other tests support iron deficiency in the setting of inflammation: a reticulocyte hemoglobin concentration of less than 28 pg or a soluble serum transferrin receptor (units: mg/L) to log ferritin (units: mcg/L) ratio of 1–8 (a ratio of less than 1 is virtually diagnostic of pure anemia of chronic disease). A functional test is hemoglobin response to oral or parenteral iron in the setting of inflammation when iron deficiency is suspected. A note of caution: certain circumstances of iron-restricted erythropoiesis (such as malignancy) will partially respond to parenteral iron infusion even when the iron stores are replete due to the immediate distribution of iron to erythropoietic progenitor cells after the infusion.

2. Other anemias of chronic disease—In the anemias of organ failure and of older adults, the iron studies are generally normal. The anemia of older persons is a diagnosis of exclusion. Clonal cytopenias of undetermined significance are diagnosed by sending a blood or bone marrow sample for myeloid gene sequencing.

Treatment

In most cases, no treatment of the anemia of chronic disease is necessary and the primary management is to address the condition causing the anemia. When the

anemia is severe or is adversely affecting the quality of life or functional status, then treatment involves either RBC transfusions or parenteral recombinant erythropoietin (epoetin alfa or darbepoetin). The FDA-approved indications for recombinant erythropoietin are hemoglobin less than 10 g/dL and anemia due to rheumatoid arthritis, IBD, hepatitis C, zidovudine therapy in HIV-infected patients, myelosuppressive chemotherapy of solid malignancy (treated with palliative intent only), or CKD (eGFR of less than 60 mL/minute). The dosing and schedule of recombinant erythropoietin are individualized to maintain the hemoglobin between 10 g/dL (100 g/L) and 12 g/dL (120 g/L). The use of recombinant erythropoietin is associated with an increased risk of venothromboembolism and arterial thrombotic episodes, especially if the hemoglobin rises to greater than 12 g/dL (120 g/L). There is concern that recombinant erythropoietin is associated with reduced survival in patients with malignancy. For patients with end-stage renal disease receiving recombinant erythropoietin who are on hemodialysis, the anemia of CKD can be more effectively corrected by adding soluble ferric pyrophosphate to their dialysate than by administering intravenous iron supplementation.

When to Refer

Referral to a hematologist is not usually necessary.

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THE THALASSEMIAS

ESSENTIALS OF DIAGNOSIS

- Microcytosis disproportionate to the degree of anemia.
- Positive family history.
- Lifelong personal history of microcytic anemia.
- Normal or elevated RBC count.
- Abnormal RBC morphology with microcytes, hypochromia, acanthocytes, and target cells.
- In beta-thalassemia, elevated levels of hemoglobin A_2 and F.

General Considerations

The thalassemias are hereditary disorders characterized by reduction in the synthesis of globin chains (alpha or beta). Reduced globin chain synthesis causes reduced hemoglobin synthesis and a hypochromic microcytic anemia because of defective hemoglobinization of RBCs. Thalassemias can be considered among the hyperproliferative hemolytic anemias, the anemias related to abnormal hemoglobin, and the hypoproliferative anemias, since all of these factors play a role in their pathophysiology. The hallmark laboratory features are small (low MCV) and pale (low mean corpuscular hemoglobin [MCH]) RBCs, anemia, and a normal to elevated RBC count (ie, a large number of the small and pale RBCs are being produced). Although patients often exhibit an elevated reticulocyte count, generally the degree of reticulocyte output is inadequate to meet the degree of RBC destruction (hemolysis) occurring in the bone marrow and the patients remain anemic.

Normal adult hemoglobin is primarily hemoglobin A, which represents approximately 98% of circulating hemoglobin. Hemoglobin A is formed from a tetramer of two alpha-globin chains and two beta-globin chains—and is designated alpha2beta2. Two copies of the alpha-globin gene are located on each chromosome 16, and there is no substitute for alpha-globin in the formation of adult hemoglobin. One copy of the beta-globin gene resides on each chromosome 11 adjacent to genes encoding the beta-like globins delta and gamma (the so-called beta-globin gene cluster region). The tetramer of alpha2delta2 forms hemoglobin A_2, which normally composes 1–3% of adult hemoglobin. The tetramer alpha2gamma2 forms hemoglobin F, which is the major hemoglobin of fetal life and which composes less than 1% of normal adult hemoglobin.

The thalassemias are described as **thalassemia trait** when there are laboratory features without significant clinical impact, **thalassemia intermedia** when there is an occasional RBC transfusion requirement or other moderate clinical impact, and **thalassemia major** when the disorder is life-threatening and the patient is transfusion-dependent. Most patients with thalassemia major die of the consequences of iron overload from RBC transfusions.

Alpha-thalassemia is due primarily to gene deletions causing reduced alpha-globin chain synthesis (Table 13–4). Each alpha-globin gene produces one-quarter of the total alpha-globin quantity, so there is a predictable proportionate decrease in alpha-globin output with each lost alpha-globin gene. Since all adult hemoglobins are alpha

Table 13–4. Alpha-thalassemia syndromes.

Number of Alpha-Globin Genes Transcribed	Syndrome	Hematocrit	MCV
4	Normal	Normal	Normal
3	Silent carrier	Normal	Normal
2	Thalassemia minor (or trait)	28–40%	60–75 fL
1	Hemoglobin H disease	22–32%	60–70 fL
0	Hydrops fetalis[1]	< 18%	< 60 fL

[1]Die in utero.
MCV, mean corpuscular volume.

Table 13–5. Beta-thalassemia syndromes.

	Beta-Globin Genes Transcribed	Hb A	Hb A_2	Hb F	Transfusions
Normal	Homozygous beta	97–99%	1–3%	< 1%	None
Thalassemia minor	Heterozygous $beta^0$	80–95%	4–8%	1–5%	None
	Heterozygous $beta^+$	80–95%	4–8%	1–5%	None
Thalassemia intermedia	Homozygous $beta^+$ (mild)	0–30%	4–8%	6–10%	Occasional
Thalassemia major	Homozygous $beta^0$	0%	4–10%	90–96%	Dependent
	Homozygous $beta^+$ (severe)	0–10%	4–10%	90–96%	Dependent

Hb, hemoglobin; $beta^0$, no beta-globin produced; $beta^+$, some beta-globin produced.

containing, alpha-thalassemia produces no change in the proportions of hemoglobins A, A_2, and F on hemoglobin electrophoresis. In severe forms of alpha-thalassemia, excess beta chains may form a beta-4 tetramer called hemoglobin H. In the presence of reduced alpha chains, the excess beta chains are unstable and precipitate, causing damage to RBC membranes. This leads to both intramedullary (bone marrow) and peripheral blood hemolysis.

Beta-thalassemias are usually caused by point mutations rather than deletions (Table 13–5). These mutations result in premature chain termination or in problems with transcription of RNA and ultimately cause reduced or absent beta-globin chain synthesis. The molecular defects leading to beta-thalassemia are numerous and heterogeneous. Defects that result in absent beta-globin chain expression are termed $beta^0$, whereas those causing reduced but not absent synthesis are termed $beta^+$. In $beta^+$ thalassemia, the degree of reduction of beta-globin synthesis is consistent within families but is quite variable between families. The reduced beta-globin chain synthesis in beta-thalassemia results in a relative increase in the proportions of hemoglobins A_2 and F compared to hemoglobin A on hemoglobin electrophoresis, as the beta-like globins (delta and gamma) substitute for the missing beta chains. In the presence of reduced beta chains, the excess alpha chains are unstable and precipitate, causing damage to RBC membranes. This leads to both intramedullary (bone marrow) and peripheral blood hemolysis. The bone marrow demonstrates erythroid hyperplasia under the stimuli of anemia and ineffective erythropoiesis (intramedullary destruction of the developing erythroid cells). In cases of severe thalassemia, the marked expansion of the erythroid compartment in the bone marrow may cause severe bony deformities, osteopenia, and pathologic bone fractures.

Clinical Findings

A. Symptoms and Signs

The **alpha-thalassemia** syndromes are seen primarily in persons from southeast Asia and China and, less commonly, in Blacks and persons of Mediterranean origin (Table 13–4). Normally, adults have four copies of the alpha-globin chain. When three alpha-globin genes are present, the patient is hematologically normal (silent carrier). When two alpha-globin genes are present, the patient is said to have **alpha-thalassemia trait,** a form of thalassemia minor. In alpha-thalassemia-1 trait, the alpha gene deletion is heterozygous (alpha –/alpha –) and affects mainly those of Asian descent. In alpha-thalassemia-2 trait, the alpha gene deletion is homozygous (alpha alpha/– –) and affects mainly Blacks. These patients are clinically normal and have a normal life expectancy and performance status, with a mild microcytic anemia. When only one alpha globin chain is present (alpha –/– –), the patient has **hemoglobin H disease** (alpha-thalassemia-3). This is a chronic hemolytic anemia of variable severity (thalassemia minor or intermedia). Physical examination might reveal pallor and splenomegaly. Affected individuals usually do not need transfusions; however, they may be required during transient periods of hemolytic exacerbation caused by infection or other stressors or during periods of erythropoietic shutdown caused by certain viruses ("aplastic crisis"). When all four alpha-globin genes are deleted, no normal hemoglobin is produced and the affected fetus is stillborn (**hydrops fetalis**). In hydrops fetalis, the only hemoglobin species made is gamma and is called hemoglobin Bart's (gamma4).

Beta-thalassemia primarily affects persons of Mediterranean origin (Italian, Greek) and to a lesser extent Asians and Blacks (Table 13–5). Patients homozygous for beta-thalassemia ($beta^0$/$beta^0$ or some with $beta^+$/$beta^+$) have **beta-thalassemia major** (Cooley anemia). Affected children are normal at birth, but after 6 months, when hemoglobin synthesis switches from hemoglobin F to hemoglobin A, severe anemia develops that requires transfusion. Numerous clinical problems ensue, including stunted growth, bony deformities (abnormal facial structure, pathologic bone fractures), hepatosplenomegaly, jaundice (due to gallstones, hepatitis-related cirrhosis, or both), and thrombophilia. The clinical course is modified significantly by transfusion therapy, but transfusional iron overload (hemosiderosis) results in a clinical picture similar to hemochromatosis, with heart failure, cardiac arrhythmias, cirrhosis, endocrinopathies, and pseudoxanthoma elasticum (calcification and fragmentation of the elastic fibers of the skin, retina, and cardiovascular system), usually after more than 100 units of RBCs have been transfused. Iron overloading occurs because the human body has no active iron excretory mechanism. Before the application of allogeneic stem cell transplantation and the development of

more effective forms of iron chelation, death from iron overload usually occurred between the ages of 20 and 30 years.

Patients homozygous for a milder form of beta-thalassemia (beta$^+$/beta$^+$, but allowing a higher rate of beta-globin synthesis) have **beta-thalassemia intermedia**. These patients have chronic hemolytic anemia but do not require transfusions except under periods of stress or during aplastic crises. They also may develop iron overload because of periodic transfusion. They survive into adult life but with hepatosplenomegaly and bony deformities. Patients heterozygous for beta-thalassemia (beta/beta^0 or beta/beta$^+$) have **beta-thalassemia minor** and a clinically insignificant microcytic anemia.

Prenatal diagnosis is available, and genetic counseling should be offered and the opportunity for prenatal diagnosis discussed.

B. Laboratory Findings

1. Alpha-thalassemia trait—These patients have mild or no anemia, with hematocrits between 28% and 40%. The MCV is strikingly low (60–75 fL) despite the modest anemia, and the red blood count is normal or increased. The peripheral blood smear shows microcytes, hypochromia, occasional target cells, and acanthocytes (cells with irregularly spaced spiked projections). The reticulocyte count and iron parameters are normal. Hemoglobin electrophoresis is normal. Alpha-thalassemia trait is thus usually diagnosed by exclusion. Genetic testing to demonstrate alpha-globin gene deletion is available.

2. Hemoglobin H disease—These patients have a more marked anemia, with hematocrits between 22% and 32%. The MCV is remarkably low (60–70 fL) and the peripheral blood smear is markedly abnormal, with hypochromia, microcytosis, target cells, and poikilocytosis. The reticulocyte count is elevated and the RBC count is normal or elevated. Hemoglobin electrophoresis will show a fast-migrating hemoglobin (hemoglobin H), which comprises 10–40% of the hemoglobin. A peripheral blood smear can be stained with supravital dyes to demonstrate the presence of hemoglobin H.

3. Beta-thalassemia minor—These patients have a modest anemia with hematocrit between 28% and 40%. The MCV ranges from 55 fL to 75 fL, and the RBC count is normal or increased. The reticulocyte count is normal or slightly elevated. The peripheral blood smear is mildly abnormal, with hypochromia, microcytosis, and target cells. In contrast to alpha-thalassemia, basophilic stippling is present. Hemoglobin electrophoresis shows an elevation of hemoglobin A_2 to 4–8% and occasional elevations of hemoglobin F to 1–5%.

4. Beta-thalassemia intermedia—These patients have a moderate anemia with hematocrit between 17% and 33%. The MCV ranges from 55 fL to 75 fL, and the RBC count is normal or increased. The reticulocyte count is elevated. The peripheral blood smear is abnormal with hypochromia, microcytosis, basophilic stippling, and target cells. Hemoglobin electrophoresis shows up to 30% hemoglobin A, an elevation of hemoglobin A_2 up to 10%, and elevation of hemoglobin F from 6% to 10%.

5. Beta-thalassemia major—These patients have severe anemia, and without transfusion the hematocrit may fall to less than 10%. The peripheral blood smear is bizarre, showing severe poikilocytosis, hypochromia, microcytosis, target cells, basophilic stippling, and nucleated RBCs. Little or no hemoglobin A is present. Variable amounts of hemoglobin A_2 are seen, and the predominant hemoglobin present is hemoglobin F.

Differential Diagnosis

Mild forms of thalassemia must be differentiated from iron deficiency. Compared to iron deficiency anemia, patients with thalassemia have a lower MCV, a normal or elevated RBC count (rather than low), a more abnormal peripheral blood smear at modest levels of anemia, and usually a reticulocytosis. Iron studies are normal, or the transferrin saturation or ferritin (or both) are elevated. Severe forms of thalassemia may be confused with other hemoglobinopathies. The diagnosis of beta-thalassemia is made by the above findings and hemoglobin electrophoresis showing elevated levels of hemoglobins A_2 and F (provided the patient is replete in iron), or beta-gene sequencing. The diagnosis of alpha-thalassemia is made by exclusion since there is no change in the proportion of the normal adult hemoglobin species or confirmed by alpha gene deletion studies. The only other microcytic anemia with a normal or elevated RBC count is iron deficiency in a patient with polycythemia vera.

Treatment

Patients with mild thalassemia (alpha-thalassemia trait or beta-thalassemia minor) require no treatment and should be identified so that they will not be subjected to repeated evaluations and mistaken treatment for iron deficiency. Patients with hemoglobin H disease should take folic acid supplementation (1 mg/day orally) and avoid medicinal iron and oxidative drugs such as sulfonamides. Patients with severe thalassemia are maintained on a regular transfusion schedule (in part to suppress endogenous erythropoiesis and therefore bone marrow expansion) and receive folic acid supplementation. Splenectomy is performed if hypersplenism causes a marked increase in the transfusion requirement or refractory symptoms. Patients with regular transfusion requirements should be treated with iron chelation (oral or parenteral) to prevent or delay life-limiting organ damage from iron overload. A new agent, **luspatercept**, has been FDA approved for transfusion-dependent beta-thalassemia. It is a TGF-beta ligand trap that promotes erythroid maturation and reduces transfusion needs.

Allogeneic stem cell transplantation is the treatment of choice for beta-thalassemia major and the only available cure. Children who have not yet experienced organ damage from iron overload do well, with long-term survival in more than 80% of cases. Autologous hematopoietic stem cell gene therapy is showing promise for thalassemia major.

When to Refer

All patients with thalassemia intermedia or major should be referred to a hematologist. Any patient with an unexplained microcytic anemia should be referred to help establish a diagnosis. Patients with thalassemia minor or intermedia should be offered genetic counseling because offspring of thalassemic couples are at risk for inheriting thalassemia major.

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VITAMIN B_{12} DEFICIENCY

ESSENTIALS OF DIAGNOSIS

- Macrocytic anemia.
- Megaloblastic blood smear (macro-ovalocytes and hypersegmented neutrophils).
- Low serum vitamin B_{12} level.

General Considerations

Vitamin B_{12} belongs to the family of cobalamins and serves as a cofactor for two important reactions in humans. As methylcobalamin, it is a cofactor for methionine synthetase in the conversion of homocysteine to methionine, and as adenosylcobalamin for the conversion of methylmalonyl-coenzyme A (CoA) to succinyl-CoA. Vitamin B_{12} comes from the diet and is present in all foods of animal origin. The daily absorption of vitamin B_{12} is 5 mcg.

The liver contains 2–5 mg of stored vitamin B_{12}. Since daily utilization is 3–5 mcg, the body usually has sufficient stores of vitamin B_{12} so that it takes more than 3 years for vitamin B_{12} deficiency to occur if all intake or absorption immediately ceases.

Since vitamin B_{12} is present in foods of animal origin, dietary vitamin B_{12} deficiency is rare but is seen in vegans—strict vegetarians who avoid all dairy products, meat, and fish (Table 13–6). Pernicious anemia is an autoimmune illness whereby autoantibodies destroy gastric parietal cells (that produce intrinsic factor) and cause atrophic gastritis or bind to and neutralize intrinsic factor, or both. Abdominal surgery may lead to vitamin B_{12} deficiency in several ways. Gastrectomy will eliminate the site of intrinsic factor production; blind loop syndrome will cause competition for vitamin B_{12} by bacterial overgrowth in the lumen of the intestine; and surgical resection of the ileum will eliminate the site of vitamin B_{12} absorption. Rare causes of vitamin B_{12} deficiency include fish tapeworm (*Diphyllobothrium latum*) infection, in which the parasite uses luminal vitamin B_{12}; pancreatic insufficiency (with failure to inactivate competing cobalamin-binding proteins [R-factors]); severe Crohn disease, causing sufficient destruction of the ileum to impair vitamin B_{12} absorption; and perhaps prolonged use of PPIs.

Table 13–6. Causes of vitamin B_{12} deficiency.

Dietary deficiency
Decreased production or availability of intrinsic factor
Pernicious anemia (autoimmune)
Gastrectomy
Helicobacter pylori infection
Competition for vitamin B_{12} in the gut
Blind loop syndrome
Fish tapeworm (rare)
Pancreatic insufficiency
PPIs
Decreased ileal absorption of vitamin B_{12}
Surgical resection
Crohn disease
Transcobalamin II deficiency (rare)

Clinical Findings

A. Symptoms and Signs

Vitamin B_{12} deficiency causes a moderate to severe anemia of slow onset; patients may have few symptoms relative to the degree of anemia. In advanced cases, the anemia may be severe, with hematocrits as low as 10–15%, and may be accompanied by leukopenia and thrombocytopenia. The deficiency also produces changes in mucosal cells, leading to glossitis, as well as other vague GI disturbances such as anorexia and diarrhea. Vitamin B_{12} deficiency also leads to a complex neurologic syndrome. Peripheral nerves are usually affected first, and patients complain initially of paresthesias. As the posterior columns of the spinal cord become impaired, patients complain of difficulty with balance or proprioception, or both. In more advanced cases, cerebral function may be altered as well, and on occasion, dementia and other neuropsychiatric abnormalities may be present. It is critical to recognize that the nonhematologic manifestations of vitamin B_{12} deficiency can be manifest despite a completely normal CBC.

Patients are usually pale and may be mildly icteric or sallow. Typically, later in the disease course, neurologic examination may reveal decreased vibration and position sense or memory disturbance (or both).

B. Laboratory Findings

The diagnosis of vitamin B_{12} deficiency is made by finding a low serum vitamin B_{12} (cobalamin) level. Whereas the normal vitamin B_{12} level is greater than 300 pg/mL (221 pmol/L), most patients with overt vitamin B_{12} deficiency have serum levels less than 200 pg/mL (148 pmol/L), with symptomatic patients often having levels less than 100 pg/mL (74 pmol/L). The diagnosis of vitamin B_{12} deficiency in low or low-normal values (level of 200–300 pg/mL [147.6–221.3 pmol/L]) is best confirmed by finding an elevated level of serum methylmalonic acid or homocysteine. Of note, elevated levels of serum methylmalonic acid can be due to kidney disease.

The anemia of vitamin B_{12} deficiency is typically moderate to severe with the MCV quite elevated (110–140 fL). However, it is possible to have vitamin B_{12} deficiency with a normal MCV from coexistent thalassemia or iron deficiency; in other cases, the reason is obscure. Patients with neurologic symptoms and signs that suggest possible vitamin B_{12} deficiency should be evaluated for that deficiency despite a normal MCV or the absence of anemia. In typical cases, the peripheral blood smear is megaloblastic, defined as RBCs that appear as macro-ovalocytes, (although other shape changes are usually present) and neutrophils that are hypersegmented (six [or greater]-lobed neutrophils or mean neutrophil lobe counts greater than four). The reticulocyte count is reduced. Because vitamin B_{12} deficiency can affect all hematopoietic cell lines, the WBC count and the platelet count are reduced in severe cases.

Other laboratory abnormalities include elevated serum LD and a modest increase in indirect bilirubin. These two findings reflect the intramedullary destruction of developing abnormal erythroid cells.

Bone marrow morphology is characteristically abnormal. Marked erythroid hyperplasia is present as a response to defective RBC production (ineffective erythropoiesis). Megaloblastic changes in the erythroid series include abnormally large cell size and asynchronous maturation of the nucleus and cytoplasm—ie, cytoplasmic maturation continues while impaired DNA synthesis causes retarded nuclear development. In the myeloid series, giant bands and meta-myelocytes are characteristically seen.

Differential Diagnosis

Vitamin B_{12} deficiency should be differentiated from folic acid deficiency, the other common cause of megaloblastic anemia, in which RBC folic acid is low while vitamin B_{12} levels are normal. The bone marrow findings of vitamin B_{12} deficiency are sometimes mistaken for a MDS or even acute erythrocytic leukemia. The distinction between vitamin B_{12} deficiency and myelodysplasia is based on the characteristic morphology and the low vitamin B_{12} and elevated methylmalonic acid levels.

Treatment

Initially, patients with vitamin B_{12} deficiency are usually treated with parenteral therapy. Intramuscular or subcutaneous injections of 100–1000 mcg of vitamin B_{12} are adequate for each dose (with the higher dose recommended initially). Replacement is usually given daily for the first week, weekly for the next month, and then monthly for life. The vitamin deficiency will recur if patients discontinue their therapy. Oral or sublingual methylcobalamin (1 mg/day) may be used instead of parenteral therapy once initial correction of the deficiency has occurred. Oral or sublingual replacement is effective, even in pernicious anemia, since approximately 1% of the dose is absorbed in the intestine via passive diffusion in the absence of active transport. It must be continued indefinitely and serum vitamin B_{12} levels must be monitored to ensure adequate replacement. For patients with neurologic symptoms caused by vitamin B_{12} deficiency, long-term parenteral vitamin B_{12} therapy is recommended, though its superiority over oral vitamin B_{12} therapy has not been proven. Because some patients are concurrently folic acid deficient from intestinal mucosal atrophy, simultaneous folic acid replacement (1 mg daily) is advised for the first several months of vitamin B_{12} replacement.

Patients respond to therapy with an immediate improvement in their sense of well-being. Hypokalemia may complicate the first several days of therapy, particularly if the anemia is severe. A brisk reticulocytosis occurs in 5–7 days, and the hematologic picture normalizes in 2 months. CNS symptoms and signs are potentially reversible if they have been present for less than 6 months. RBC transfusions are rarely needed despite the severity of anemia, but when given, diuretics are also recommended to avoid heart failure because this anemia develops slowly and the plasma volume is increased at the time of diagnosis.

When to Refer

Referral to a hematologist is not usually necessary.

Lewis CA et al. Iron, vitamin B_{12}, folate and copper deficiency after bariatric surgery and the impact on anaemia: a systematic review. Obes Surg. 2020;30:4542. [PMID: 32785814]

Socha DS et al. Severe megaloblastic anemia: vitamin deficiency and other causes. Cleve Clin J Med. 2020;87:153. [PMID: 32127439]

Wolffenbuttel BHR et al. The many faces of cobalamin (vitamin B_{12}) deficiency. Mayo Clin Proc Innov Qual Outcomes. 2019;3:200. [PMID: 31193945]

FOLIC ACID DEFICIENCY

ESSENTIALS OF DIAGNOSIS

- Macrocytic anemia.
- Megaloblastic blood smear (macro-ovalocytes and hypersegmented neutrophils).
- Reduced folic acid levels in RBCs or serum.
- Normal serum vitamin B_{12} level.

General Considerations

"Folic acid" is the term commonly used for pteroylmonoglutamic acid. Folic acid is present in most fruits and vegetables (especially citrus fruits and green leafy vegetables). Daily dietary requirements are 50–100 mcg. Total body stores of folic acid are approximately 5 mg, enough to supply requirements for 2–3 months.

The most common cause of folic acid deficiency is inadequate dietary intake (Table 13–7). Alcoholic or anorectic patients, persons who do not eat fresh fruits and vegetables, and those who overcook their food are candidates for folic acid deficiency. Reduced folic acid absorption is rarely seen, since absorption occurs from the entire GI tract. However, medications such as phenytoin, trimethoprim-sulfamethoxazole, or sulfasalazine may interfere with its absorption. Folic acid absorption is poor in some

Table 13–7. Causes of folic acid deficiency.

Dietary deficiency
Decreased absorption
Celiac disease
Medications: phenytoin, sulfasalazine, trimethoprim-sulfamethoxazole
Concurrent vitamin B_{12} deficiency
Increased requirement
Chronic hemolytic anemia
Pregnancy
Exfoliative skin disease
Excess loss: hemodialysis
Inhibition of reduction to active form
Methotrexate

patients with vitamin B_{12} deficiency due to GI mucosal atrophy. Folic acid requirements are increased in pregnancy, hemolytic anemia, and exfoliative skin disease, and in these cases the increased requirements (5–10 times normal) may not be met by a normal diet.

Clinical Findings

A. Symptoms and Signs

The clinical features are similar to those of vitamin B_{12} deficiency. However, isolated folic acid deficiency does not result in neurologic abnormalities.

B. Laboratory Findings

Megaloblastic anemia is identical to anemia resulting from vitamin B_{12} deficiency. A RBC folic acid level below 150 ng/mL (340 nmol/L) is diagnostic of folic acid deficiency. Whether to order a serum or a RBC folate level remains unsettled since there are few, if any, data to support one test over the other. Usually the serum vitamin B_{12} level is normal, but it should always be measured when folic acid deficiency is suspected. In some instances, folic acid deficiency is a consequence of the GI mucosal atrophy from vitamin B_{12} deficiency.

Differential Diagnosis

The megaloblastic anemia of folic acid deficiency should be differentiated from vitamin B_{12} deficiency by the finding of a normal vitamin B_{12} level and a reduced RBC (or serum) folic acid level. Alcoholic patients, who often have nutritional deficiency, may also have anemia of liver disease. Pure anemia of liver disease causes a macrocytic anemia but does not produce megaloblastic morphologic changes in the peripheral blood; rather, target cells are present. Hypothyroidism is associated with mild macrocytosis and also with pernicious anemia.

Treatment

Folic acid deficiency is treated with daily oral folic acid (1 mg). The response is similar to that seen in the treatment of vitamin B_{12} deficiency, with rapid improvement and a sense of well-being, reticulocytosis in 5–7 days, and total correction of hematologic abnormalities within 2 months. Large doses of folic acid may produce hematologic responses in cases of vitamin B_{12} deficiency, but permit neurologic damage to progress; hence, obtaining a serum vitamin B_{12} level in suspected folic acid deficiency is paramount.

When to Refer

Referral to a hematologist is not usually necessary.

Lewis CA et al. Iron, vitamin B_{12}, folate and copper deficiency after bariatric surgery and the impact on anaemia: a systematic review. Obes Surg. 2020;30:4542. [PMID: 32785814]
Shulpekova Y et al. The concept of folic acid in health and disease. Molecules. 2021;26:3731. [PMID: 34207319]
Socha DS et al. Severe megaloblastic anemia: vitamin deficiency and other causes. Cleve Clin J Med. 2020;87:153. [PMID: 32127439]

HEMOLYTIC ANEMIAS

The hemolytic anemias are a group of disorders in which RBC survival is reduced, either episodically or continuously. The bone marrow has the ability to increase erythroid production up to eightfold in response to reduced RBC survival, so anemia will be present only when the ability of the bone marrow to compensate is outstripped. This will occur when RBC survival is extremely short or when the ability of the bone marrow to compensate is impaired.

Hemolytic disorders are generally classified according to whether the defect is intrinsic to the RBC or due to some external factor (Table 13–8). Intrinsic defects have been described in all components of the RBC, including the membrane, enzyme systems, and hemoglobin; most of these disorders are hereditary. Hemolytic anemias due to external factors are classified as immune,

Table 13–8. Classification of hemolytic anemias.

Intrinsic
Membrane defects: hereditary spherocytosis, hereditary elliptocytosis, paroxysmal nocturnal hemoglobinuria
Glycolytic defects: pyruvate kinase deficiency, severe hypophosphatemia
Oxidation vulnerability: glucose-6-phosphate dehydrogenase deficiency, methemoglobinemia
Hemoglobinopathies: sickle cell syndromes, thalassemia, unstable hemoglobins
Extrinsic
Immune: autoimmune, lymphoproliferative disease, drug-induced, idiopathic
Microangiopathic: thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, valve hemolysis, metastatic adenocarcinoma, vasculitis, copper overload
Infection: *Plasmodium, Clostridium, Borrelia*
Hypersplenism
Burns

microangiopathic hemolytic anemias, drug-induced, and RBC infections.

Certain laboratory features are common to all hemolytic anemias. Haptoglobin, a normal plasma protein that binds and clears free hemoglobin released into plasma, is depressed in hemolytic disorders. However, the haptoglobin level is influenced by many factors and is not always a reliable indicator of hemolysis, particularly in end-stage liver disease (its site of synthesis). When intravascular hemolysis occurs, transient hemoglobinemia ensues. Hemoglobin is filtered through the renal glomerulus and is usually reabsorbed by tubular cells. Hemoglobinuria will be present only when the capacity for reabsorption of hemoglobin by renal tubular cells is exceeded. In the absence of hemoglobinuria, evidence for prior intravascular hemolysis is the presence of hemosiderin in shed renal tubular cells (positive urine hemosiderin). With severe intravascular hemolysis, hemoglobinemia and methemalbuminemia may be present. Hemolysis increases the indirect bilirubin, and the total bilirubin may rise to 4 mg/dL (68 mcmol/L) or more. Bilirubin levels higher than this may indicate some degree of hepatic dysfunction. Serum LD levels are strikingly elevated in cases of microangiopathic hemolysis (thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome) and may be elevated in other hemolytic anemias.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

ESSENTIALS OF DIAGNOSIS

- Episodic hemoglobinuria.
- Thrombosis is common.
- Suspect in confusing cases of hemolytic anemia with or without pancytopenia.
- Flow cytometry demonstrates deficiencies of CD55 and CD59.

General Considerations

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired clonal hematopoietic stem cell disorder that results in abnormal sensitivity of the RBC membrane to lysis by complement and therefore hemolysis. Free hemoglobin is released into the blood that scavenges nitric oxide and promotes esophageal spasms, male erectile dysfunction, kidney damage, and thrombosis. Patients with significant PNH have shortened survival; thrombosis is the primary cause of death.

Clinical Findings

A. Symptoms and Signs

Classically, patients report episodic hemoglobinuria resulting in reddish-brown urine. Hemoglobinuria is most often noticed in the first morning urine due to the fall in blood pH while sleeping (hypoventilation) that facilitates this hemolysis. Besides anemia, these patients are prone to thrombosis, especially within mesenteric and hepatic veins, CNS veins (sagittal vein), and skin vessels (with formation of painful nodules). As this is a hematopoietic stem cell disorder, PNH may appear de novo or arise in the setting of aplastic anemia or myelodysplasia with possible progression to acute myeloid leukemia (AML). It is common that patients with idiopathic aplastic anemia have a small PNH clone (less than 2%) on blood or bone marrow analysis; this should not be considered true PNH per se, especially in the absence of a reticulocytosis or thrombosis.

B. Laboratory Findings

Anemia is of variable severity and frequency, so reticulocytosis may or may not be present at any given time. Abnormalities on the blood smear are nondiagnostic but may include macro-ovalocytes and polychromasia. Since the episodic hemolysis is mainly intravascular, urine hemosiderin is a useful test. Serum LD is characteristically quite elevated. Iron deficiency is commonly present, related to chronic iron loss from hemoglobinuria.

The WBC count and platelet count may be decreased and are always decreased in the setting of aplastic anemia. The best screening test is flow cytometry of blood erythrocytes, granulocytes, and monocytes to demonstrate deficiency of CD55 and CD59. The proportion of erythrocytes deficient in these proteins might be low due to the ongoing destruction of affected erythrocytes. The FLAER assay (fluorescein-labeled proaerolysin) by flow cytometry is more sensitive. Bone marrow morphology is variable and may show either generalized hypoplasia or erythroid hyperplasia or both. The bone marrow karyotype may be either normal or demonstrate a clonal abnormality.

Treatment

Many patients with PNH have mild disease not requiring intervention. In severe cases and in those occurring in the setting of myelodysplasia or previous aplastic anemia, allogeneic hematopoietic stem cell transplantation may prove curative. In patients with severe hemolysis (usually requiring RBC transfusions) or thrombosis (or both), treatment with eculizumab is warranted. Eculizumab is a humanized monoclonal antibody against complement protein C5 given every 2 weeks. Binding of eculizumab to C5 prevents its cleavage so the membrane attack complex cannot assemble. Eculizumab improves quality of life and reduces hemolysis, transfusion requirements, fatigue, and thrombosis risk. Eculizumab increases the risk of *Neisseria meningitidis* infections; patients receiving the antibody should undergo meningococcal vaccination (including vaccines for serogroup B) and take oral penicillin (or equivalent) meningococcal prophylaxis. Ravulizumab is a longer-acting version of eculizumab; it is given every 8 weeks and demonstrates fewer breakthrough hemolytic episodes than eculizumab. A C3 inhibitor, pegcetacoplan, is also available for PNH and blocks both intra- and extravascular hemolysis pathways. Iron replacement is indicated for treatment of iron deficiency when present, which may improve the

anemia while also causing a transient increase in hemolysis. For unclear reasons, corticosteroids are effective in decreasing hemolysis.

When to Refer

Most patients with PNH should be under the care of a hematologist.

Brodsky RA. How I treat paroxysmal nocturnal hemoglobinuria. Blood. 2021;137:1304. [PMID: 33512400]
Hillmen P et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2021;384:1028. [PMID: 33730455]
Patriquin CJ et al. How we treat paroxysmal nocturnal hemoglobinuria: a consensus statement of the Canadian PNH Network and review of the national registry. Eur J Haematol. 2019;102:36. [PMID: 30242915]

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

ESSENTIALS OF DIAGNOSIS

- X-linked recessive disorder seen commonly in American Black men.
- Episodic hemolysis in response to oxidant drugs or infection.
- Bite cells and blister cells on the peripheral blood smear.
- Reduced levels of glucose-6-phosphate dehydrogenase between hemolytic episodes.

General Considerations

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a hereditary enzyme defect that causes episodic hemolytic anemia because of the decreased ability of RBCs to deal with oxidative stresses. G6PD deficiency leads to excess oxidized glutathione that forces hemoglobin to denature and form precipitants called Heinz bodies. Heinz bodies cause RBC membrane damage, which leads to premature removal of these RBCs by reticuloendothelial cells within the spleen (ie, extravascular hemolysis).

Numerous G6PD isoenzymes have been described. The usual isoenzyme found in American Blacks is designated G6PD-A and that found in Whites is designated G6PD-B, both of which have normal function and stability and therefore no hemolytic anemia. Ten to 15 percent of American Blacks have the variant G6PD isoenzyme designated A–, in which there is both a reduction in normal enzyme activity and a reduction in its stability. The A– isoenzyme activity declines rapidly as the RBC ages past 40 days, a fact that explains the clinical findings in this disorder. More than 150 G6PD isoenzyme variants have been described, including some Mediterranean, Ashkenazi Jewish, and Asian variants with very low enzyme activity, episodic hemolysis, and exacerbations due to oxidizing substances including fava beans. Patients with G6PD deficiency seem to be protected from malaria parasitic infection, have less CAD, and possibly have fewer cancers and greater longevity.

Clinical Findings

G6PD deficiency is an X-linked disorder affecting 10–15% of American hemizygous Black males and rare female homozygotes. Female carriers are rarely affected—only when an unusually high percentage of cells producing the normal enzyme are X-inactivated.

A. Symptoms and Signs

Patients are usually healthy, without chronic hemolytic anemia or splenomegaly. Hemolysis occurs episodically due to oxidative stress on the RBCs, generated either by infection or exposure to certain medications. Medications initiating hemolysis that should be avoided include dapsone, methylene blue, phenazopyridine, primaquine, rasburicase, toluidine blue, nitrofurantoin, trimethoprim/sulfamethoxazole, sulfadiazine, pegloticase, and quinolones. Other medications, such as chloroquine, quinine, high-dose aspirin, and isoniazid, have been implicated but are less certain as offenders since they are often given during infections. Even with continuous use of the offending medication, the hemolytic episode is self-limited because older RBCs (with low enzyme activity) are removed and replaced with a population of young RBCs (reticulocytes) with adequate functional levels of G6PD. Severe G6PD deficiency (as in Mediterranean variants) may produce a chronic hemolytic anemia.

B. Laboratory Findings

Between hemolytic episodes, the blood is normal. During episodes of hemolysis, the hemoglobin rarely falls below 8 g/dL (80 g/L), and there is reticulocytosis and increased serum indirect bilirubin. The peripheral blood cell smear often reveals a small number of "bite" cells—cells that appear to have had a bite taken out of their periphery, or "blister" cells. This indicates pitting of precipitated membrane hemoglobin aggregates (ie, Heinz bodies) by the splenic macrophages. Heinz bodies may be demonstrated by staining a peripheral blood smear with cresyl violet; they are not visible on the usual Wright-Giemsa–stained blood smear. Specific enzyme assays for G6PD reveal a low level but may be falsely normal if they are performed during or shortly after a hemolytic episode during the period of reticulocytosis. In these cases, the enzyme assays should be repeated weeks after hemolysis has resolved. In severe cases of G6PD deficiency, enzyme levels are always low.

Treatment

No treatment is necessary except to avoid known oxidant medications.

Garcia AA et al. Treatment strategies for glucose-6-phosphate dehydrogenase deficiency: past and future perspectives. Trends Pharmacol Sci. 2021;42:829. [PMID: 34389161]

Georgakouli K et al. Exercise in glucose-6-phosphate dehydrogenase deficiency: harmful or harmless? A narrative review. Oxid Med Cell Longev. 2019;2019:8060193. [PMID: 31089417]

SICKLE CELL ANEMIA & RELATED SYNDROMES

ESSENTIALS OF DIAGNOSIS

- Recurrent pain episodes.
- Positive family history and lifelong history of hemolytic anemia.
- Irreversibly sickled cells on peripheral blood smear.
- Hemoglobin S is the major hemoglobin seen on electrophoresis.

General Considerations

Sickle cell anemia is an autosomal recessive disorder in which an abnormal hemoglobin leads to chronic hemolytic anemia with numerous clinical consequences. A single DNA base change leads to an amino acid substitution of valine for glutamate in the sixth position on the beta-globin chain. The abnormal beta chain is designated beta^s and the tetramer of alpha-2beta^s-2 is designated hemoglobin SS. Hemoglobin S is unstable and polymerizes in the setting of various stressors, including hypoxemia and acidosis, leading to the formation of sickled RBCs. Sickled cells result in hemolysis and the release of ATP, which is converted to adenosine. Adenosine binds to its receptor (A2B), resulting in the production of 2,3-biphosphoglycerate and the induction of more sickling, and to its receptor (A2A) on natural killer cells, resulting in pulmonary inflammation. The free hemoglobin from hemolysis scavenges nitric oxide causing endothelial dysfunction, vascular injury, and pulmonary hypertension.

The rate of sickling is influenced by the intracellular concentration of hemoglobin S and by the presence of other hemoglobins within the cell. Hemoglobin F cannot participate in polymer formation, and its presence markedly retards sickling. Factors that increase sickling are RBC dehydration and factors that lead to formation of deoxyhemoglobin S (eg, acidosis and hypoxemia), either systemic or local in tissues. Hemolytic crises may be related to splenic sequestration of sickled cells (primarily in childhood before the spleen has been infarcted as a result of repeated sickling) or with coexistent disorders such as G6PD deficiency.

The beta^S gene is carried in 8% of American Blacks, and 1 of 400 American Black children will be born with sickle cell anemia; prenatal diagnosis is available when sickle cell anemia is suspected. Genetic counseling should be made available to patients.

Clinical Findings

A. Symptoms and Signs

The disorder has its onset during the first year of life, when hemoglobin F levels fall as a signal is sent to switch from production of gamma-globin to beta-globin. Chronic hemolytic anemia produces jaundice, pigment (calcium bilirubinate) gallstones, splenomegaly (early in life), and poorly healing skin ulcers over the lower tibia. Life-threatening severe anemia can occur during hemolytic or aplastic crises, the latter generally associated with viral or other infection caused by immunoincompetence from hyposplenism or by folic acid deficiency causing reduced erythropoiesis.

Acute painful episodes due to acute vaso-occlusion from clusters of sickled RBCs may occur spontaneously or be provoked by infection, dehydration, or hypoxia. Common sites of acute painful episodes include the spine and long appendicular bones. These episodes last hours to days and may produce low-grade fever. Acute vaso-occlusion may cause strokes due to sagittal sinus venous thrombosis or to bland or hemorrhagic CNS arterial ischemia. Vaso-occlusion may also cause priapism. Vaso-occlusive episodes are not associated with increased hemolysis.

Repeated episodes of vascular occlusion especially affect the heart, lungs, and liver. The acute chest syndrome is characterized by acute chest pain, hypoxemia, and pulmonary infiltrates on a chest radiograph and must be distinguished from an infectious pneumonia. Ischemic necrosis of bones may occur, rendering the bone susceptible to osteomyelitis due to salmonellae and (somewhat less commonly) staphylococci. Infarction of the papillae of the renal medulla causes renal tubular concentrating defects and gross hematuria, more often encountered in sickle cell trait than in sickle cell anemia. Retinopathy is often present and may lead to visual impairment. Pulmonary hypertension may develop and is associated with a poor prognosis. These patients are prone to delayed puberty. An increased incidence of infection is related to hyposplenism as well as to defects in the alternate complement pathway.

On examination, patients are often chronically ill and jaundiced. There is often hepatomegaly, but the spleen is not palpable in adult life. The heart may be enlarged with a hyperdynamic precordium and systolic murmurs and, in some cases, a pronounced increase in P2. Nonhealing cutaneous ulcers of the lower leg and retinopathy may be present.

B. Laboratory Findings

Chronic hemolytic anemia is present. The hematocrit is usually 20–30%. The peripheral blood smear is characteristically abnormal, with sickled cells comprising 5–50% of RBCs. Other findings include reticulocytosis (10–25%), nucleated RBCs, and hallmarks of hyposplenism such as Howell-Jolly bodies and target cells. The WBC count is characteristically elevated to 12,000–15,000/mcL (12–15 × 10^9/L), and reactive thrombocytosis may occur. Indirect bilirubin levels are high.

The diagnosis of sickle cell anemia is confirmed by hemoglobin electrophoresis (Table 13–9). Hemoglobin S will usually comprise 85–98% of hemoglobin. In homozygous S disease, no hemoglobin A will be present. Hemoglobin F levels are sometimes increased, and high hemoglobin F levels (15–20%) are associated with a more benign

Table 13–9. Hemoglobin distribution in sickle cell syndromes.

Genotype	Clinical Diagnosis	Hb A	Hb S	Hb A_2	Hb F
AA	Normal	97–99%	0%	1–2%	< 1%
AS	Sickle trait	60%	40%	1–2%	< 1%
AS, alpha-thalassemia	Sickle trait, alpha-thalassemia	70–75%	25–30%	1–2%	< 1%
SS	Sickle cell anemia	0%	86–98%	1–3%	5–15%
SS, alpha-thalassemia (3 genes)	SS alpha-thalassemia, silent	0%	90%	3%	7–9%
SS, alpha-thalassemia (2 genes)	SS alpha-thalassemia, trait	0%	80%	3%	11–21%
S, $beta^0$-thalassemia	Sickle $beta^0$-thalassemia	0%	70–80%	3–5%	10–20%
S, $beta^+$-thalassemia	Sickle $beta^+$-thalassemia	10–20%	60–75%	3–5%	10–20%

Hb, hemoglobin; $beta^0$, no beta-globin produced; $beta^+$, some beta-globin produced.

clinical course. Patients with S-$beta^+$-thalassemia and SS alpha-thalassemia also have a more benign clinical course than straight sickle cell anemia (SS) patients.

Treatment

When allogeneic hematopoietic stem cell transplantation is performed before the onset of significant end-organ damage, it can cure more than 80% of children with sickle cell anemia who have suitable HLA-matched donors, with a reasonably good quality of life. Transplantation remains investigational in adults. Other therapies modulate disease severity: hydroxyurea increases hemoglobin F levels epigenetically. Hydroxyurea (500–750 mg orally daily) reduces the frequency of painful crises in patients whose quality of life is disrupted by frequent vaso-occlusive pain episodes (three or more per year). Long-term follow-up of patients taking hydroxyurea demonstrates it improves overall survival and quality of life with little evidence for secondary malignancy. The use of omega-3 (n-3) fatty acid supplementation may also reduce vaso-occlusive episodes and reduce transfusion needs in patients with sickle cell anemia. L-glutamine has been shown to favorably modulate sickle pain crises and acute chest syndrome. A monoclonal antibody (crizanlizumab-tmca) reduces vaso-occlusive episodes by 50%. It blocks P-selectin on activated endothelial cells and thus disrupts the adverse interactions of platelets, RBCs, and leukocytes with the endothelial wall. Voxelotor inhibits the polymerization of deoxygenated sickle RBCs and increases the hemoglobin in SS patients age 12 years or older, and thus can reduce transfusion needs.

Supportive care is the mainstay of treatment for sickle cell anemia. Patients are maintained on folic acid supplementation (1 mg orally daily) and given transfusions for aplastic or hemolytic crises. When acute painful episodes occur, precipitating factors should be identified and infections treated if present. The patient should be kept well hydrated, given generous analgesics, and supplied oxygen if hypoxic. Pneumococcal vaccination reduces the incidence of infections with this pathogen while hydroxyurea and L-glutamine reduce hospitalizations for acute pain. ACE inhibitors are recommended in patients with microalbuminuria.

Exchange transfusions are indicated for the treatment of severe or intractable acute vaso-occlusive crises, acute chest syndrome, priapism, and stroke. Long-term transfusion therapy has been shown to be effective in reducing the risk of recurrent stroke in children. Phenotypically matched transfused RBCs are recommended to reduce the risk of RBC alloimmunization. It has been recommended that children with SS who are aged 2–16 years have annual transcranial ultrasounds and, if the Doppler velocity is abnormal (200 cm/s or greater), the clinician should strongly consider beginning transfusions to prevent stroke. Iron chelation is needed for those on chronic transfusion therapy.

Prognosis

Sickle cell anemia becomes a chronic multisystem disease, leading to organ failure that may result in early death. With improved supportive care, average life expectancy is now between 40 and 50 years of age.

When to Refer

Patients with sickle cell anemia should have their care coordinated with a hematologist and should be referred to a Comprehensive Sickle Cell Center, if available.

When to Admit

Patients should be admitted for management of acute chest syndrome, for aplastic crisis, or for painful episodes that do not respond to outpatient interventions.

DeBaun MR et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Adv. 2020;4:1554. [PMID: 32298430]

Howard J et al. Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol. 2021;8:e323. [PMID: 33838113]

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Pecker LH et al. Sickle cell disease. Ann Intern Med. 2021;174:ITC1. [PMID: 33428443]
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SICKLE CELL TRAIT

People with the heterozygous hemoglobin genotype AS have **sickle cell trait.** These persons are hematologically normal, with no anemia and normal RBCs on peripheral blood smear. Hemoglobin electrophoresis will reveal that approximately 40% of hemoglobin is hemoglobin S (Table 13–9). People with sickle cell trait experience more rhabdomyolysis during vigorous exercise but do not have increased mortality compared to the general population. They may be at increased risk for venous thromboembolism. Chronic sickling of RBCs in the acidotic renal medulla results in microscopic and gross hematuria, hyposthenuria (poor urine concentrating ability), and possibly CKD. No treatment is necessary but genetic counseling is recommended.

Liem RI. Balancing exercise risk and benefits: lessons learned from sickle cell trait and sickle cell anemia. Hematology Am Soc Hematol Educ Program. 2018;2018:418. [PMID: 30504341]
Pecker LH et al. The current state of sickle cell trait: implications for reproductive and genetic counseling. Hematology Am Soc Hematol Educ Program. 2018;2018:474. [PMID: 30504348]

SICKLE THALASSEMIA

Patients with homozygous sickle cell anemia and alpha-thalassemia have less vigorous hemolysis and run higher hemoglobins than SS patients due to reduced RBC sickling related to a lower hemoglobin concentration within the RBC and higher hemoglobin F levels (Table 13–9). The MCV is low, and the RBCs are hypochromic.

Patients who are compound heterozygotes for beta^s and beta-thalassemia are clinically affected with sickle cell syndromes. Sickle beta^0-thalassemia is clinically very similar to homozygous SS disease. Vaso-occlusive crises may be somewhat less severe, and the spleen is not always infarcted. The MCV is low, in contrast to the normal MCV of sickle cell anemia. Hemoglobin electrophoresis reveals no hemoglobin A but will show an increase in hemoglobins A_2 and F (Table 13–9).

Sickle beta$^+$-thalassemia is a milder disorder than homozygous SS disease, with fewer pain episodes but more acute chest syndrome than sickle beta^0-thalassemia. The spleen is usually palpable. The hemolytic anemia is less severe, and the hematocrit is usually 30–38%, with reticulocytes of 5–10%. Hemoglobin electrophoresis shows the presence of some hemoglobin A and elevated hemoglobins A_2 and F (Table 13–9). The MCV is low.

AUTOIMMUNE HEMOLYTIC ANEMIA

ESSENTIALS OF DIAGNOSIS

- Acquired hemolytic anemia caused by IgG autoantibody.
- Spherocytes and reticulocytosis on peripheral blood smear.
- Positive antiglobulin (Coombs) test.

General Considerations

Warm autoimmune hemolytic anemia is an acquired disorder in which an IgG autoantibody is formed that binds to a RBC membrane protein and does so most avidly at body temperature (ie, a "warm" autoantibody). The antibody is most commonly directed against a basic component of the Rh system present on RBCs. When IgG antibodies coat the RBC, the Fc portion of the antibody is recognized by macrophages present in the spleen and other portions of the reticuloendothelial system. The interaction between splenic macrophages and the antibody-coated RBC results in removal of RBC membrane and the formation of a spherocyte due to the decrease in surface-to-volume ratio of the surviving RBC. These spherocytic cells have decreased deformability and are unable to squeeze through the 2-mcm fenestrations of splenic sinusoids and become trapped in the red pulp of the spleen. When large amounts of IgG are present on RBCs, complement may be fixed. Direct complement lysis of cells is rare, but the presence of C3b on the surface of RBCs allows Kupffer cells in the liver to participate in the hemolytic process via C3b receptors. The destruction of RBCs in the spleen and liver designates this as extravascular hemolysis. The clinical distinction between extra- and intravascular hemolysis is not always straightforward.

Approximately one-half of all cases of autoimmune hemolytic anemia are idiopathic. The disorder may also be seen in association with SLE, other rheumatic disorders, chronic lymphocytic leukemia (CLL), or lymphomas. It must be distinguished from drug-induced hemolytic anemia. When penicillin (or other medications, especially cefotetan, ceftriaxone, and piperacillin) coats the RBC membrane, the autoantibody is directed against the membrane-drug complex. Fludarabine, an antineoplastic, causes autoimmune hemolytic anemia through immunoincompetence: there is defective self- versus non–self-immune surveillance permitting the escape of a B-cell clone, which produces the offending autoantibody.

Clinical Findings

A. Symptoms and Signs

Autoimmune hemolytic anemia typically produces an anemia of rapid onset that may be life-threatening. Patients complain of fatigue and dyspnea and may present with angina pectoris or heart failure. On examination, jaundice and splenomegaly are usually present.

B. Laboratory Findings

The anemia is of variable degree but may be very severe, with hematocrit of less than 10%. Reticulocytosis is present, and spherocytes are seen on the peripheral blood smear. In cases of severe hemolysis, the stressed bone marrow may also release nucleated RBCs. As with other hemolytic disorders, the serum indirect bilirubin is increased and the haptoglobin is low. Approximately 10% of patients with autoimmune hemolytic anemia have coincident immune thrombocytopenia (Evans syndrome).

The antiglobulin (Coombs) test forms the basis for diagnosis. The Coombs reagent is a rabbit IgM antibody raised against human IgG or human complement. The direct antiglobulin (Coombs) test (DAT) is performed by mixing the patient's RBCs with the Coombs reagent and looking for agglutination, which indicates the presence of IgG or both IgG and complement on the RBC surface. The indirect antiglobulin (Coombs) test is performed by mixing the patient's serum with a panel of type O RBCs. After incubation of the test serum and panel RBCs, the Coombs reagent is added. Agglutination in this system indicates the presence of free antibody (autoantibody or alloantibody) in the patient's serum.

The direct antiglobulin test is positive (for IgG or both IgG and complement) in about 90% of patients with autoimmune hemolytic anemia. A "super-Coombs" test might be positive in some of the 10% negative group. The indirect antiglobulin test may or may not be positive. A positive indirect antiglobulin test indicates the presence of a large amount of autoantibody that has saturated binding sites on the RBC and consequently appears in the serum. Because the patient's serum usually contains the autoantibody, it may be difficult to obtain a "compatible" cross-match with homologous RBCs for transfusions since the cross-match indicates the possible presence (true or false) of a RBC "alloantibody."

Treatment

Initial treatment consists of oral prednisone, 1–2 mg/kg/day. Patients with DAT-negative and DAT-positive warm autoimmune hemolysis respond equally well to corticosteroids. Transfused RBCs will survive similarly as the patient's own RBCs (ie, shortened survival). Because of difficulty in performing the cross-match, possible "incompatible" blood may need to be given. Decisions regarding transfusions should be made in consultation with a hematologist and a blood bank specialist. Death from cardiovascular collapse can occur in the setting of rapid hemolysis. In patients with rapid hemolysis, therapeutic plasmapheresis should be performed early in management to remove autoantibodies.

Patients with warm autoimmune hemolytic anemia refractory to prednisone may also be treated with a variety of agents. Treatment with rituximab, a monoclonal antibody against the B cell antigen CD20, is effective in many cases. The suggested dose is 375 mg/m^2 intravenously weekly for 4 weeks. Rituximab is used in conjunction with corticosteroids as initial therapy in some patients with severe disease. In patients with past hepatitis B virus (HBV) infection, rituximab should be used with an anti-HBV agent since HBV reactivation, fulminant hepatitis and, rarely, death can otherwise occur. Danazol, 400–800 mg/day orally, is less often effective than in immune thrombocytopenia but is well suited for long-term use because of its low toxicity profile. Immunosuppressive agents, including cyclophosphamide, vincristine, azathioprine, mycophenolate mofetil, alemtuzumab (an anti-CD52 antibody), or cyclosporine, may also be used. High-dose intravenous immune globulin (1 g/kg daily for 2 days) may be effective in controlling hemolysis, but the benefit is short-lived (1–3 weeks) and immune globulin is very expensive. If prednisone or other medical therapies are ineffective, splenectomy can be considered, which may cure the disorder. The long-term prognosis for patients with this disorder is good, especially if there is no other underlying autoimmune disorder or lymphoproliferative disorder. Treatment of an associated lymphoproliferative disorder will also treat the hemolytic anemia.

When to Refer

Patients with autoimmune hemolytic anemia should be referred to a hematologist for confirmation of the diagnosis and subsequent care.

When to Admit

Patients should be hospitalized for symptomatic anemia or rapidly falling hemoglobin levels.

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Hill QA et al. Defining autoimmune hemolytic anemia: a systematic review of the terminology used for diagnosis and treatment. Blood Adv. 2019;3:1897. [PMID: 31235526]
Jäger U et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the First International Consensus Meeting. Blood Rev. 2020;41:100648. [PMID: 31839434]

COLD AGGLUTININ DISEASE

ESSENTIALS OF DIAGNOSIS

- Increased reticulocytes on peripheral blood smear.
- Antiglobulin (Coombs) test positive only for complement.
- Positive cold agglutinin titer.

General Considerations

Cold agglutinin disease is an acquired hemolytic anemia due to an IgM autoantibody (called a "cold agglutinin") usually directed against the I/i antigen on RBCs. These IgM autoantibodies characteristically will react poorly with cells at 37°C but avidly at lower temperatures, usually at 0–4°C

(ie, "cold" autoantibody). Since the blood temperature (even in the most peripheral parts of the body) rarely goes lower than 20°C, only cold autoantibodies reactive at relatively higher temperatures will produce clinical effects. Hemolysis results indirectly from attachment of IgM, which in the cooler parts of the circulation (fingers, nose, ears) binds and fixes complement. When the RBC returns to a warmer temperature, the IgM antibody dissociates, leaving complement on the cell. Complement lysis of RBCs rarely occurs. Rather, C3b, present on the RBCs, is recognized by Kupffer cells (which have receptors for C3b), and RBC sequestration and destruction in the liver ensues (extravascular hemolysis). However, in some cases, the complement membrane attack complex forms, lysing the RBCs (intravascular hemolysis). The clinical distinction between extra- and intra-vascular hemolysis is not always straightforward.

Most cases of chronic cold agglutinin disease are idiopathic. Others occur in association with Waldenström macroglobulinemia, lymphoma, or CLL, in which a monoclonal IgM paraprotein is produced. Acute postinfectious cold agglutinin disease occurs following mycoplasma pneumonia or viral infection (infectious mononucleosis, measles, mumps, or cytomegalovirus [CMV] with autoantibody directed against antigen i rather than I).

Clinical Findings

A. Symptoms and Signs

In chronic cold agglutinin disease, symptoms related to RBC agglutination occur on exposure to cold, and patients may complain of mottled or numb fingers or toes, acrocyanosis, episodic low back pain, and dark-colored urine. Hemolytic anemia is occasionally severe, but episodic hemoglobinuria may occur on exposure to cold. The hemolytic anemia in acute postinfectious syndromes is rarely severe.

B. Laboratory Findings

Mild anemia is present with reticulocytosis and rarely spherocytes. The blood smear made at room temperature shows agglutinated RBCs (there is no agglutination on a blood smear made at body temperature). The direct antiglobulin (Coombs) test will be positive for complement only. Serum cold agglutinin titer will semi-quantitate the autoantibody. A monoclonal IgM is often found on serum protein electrophoresis and confirmed by serum immunoelectrophoresis. There is indirect hyperbilirubinemia and the haptoglobin is low during periods of hemolysis. Serum free hemoglobin is often elevated, and hemoglobinuria is present when intravascular hemolysis is occurring.

Treatment

Treatment is largely symptomatic, based on avoiding exposure to cold. Splenectomy and prednisone are usually ineffective (except when associated with a lymphoproliferative disorder) since hemolysis takes place in the liver and blood stream. Rituximab is the treatment of choice but in patients with past HBV infection, it must be used with anti-HBV prophylaxis. The rituximab dose is 375 mg/m^2 intravenously weekly for 4 weeks. Relapses may be effectively retreated. High-dose intravenous immunoglobulin (2 g/kg) may be temporarily effective, but it is rarely used because of the high cost and short duration of benefit. Patients with severe disease may be treated with cytotoxic agents, such as bendamustine (plus rituximab), cyclophosphamide, fludarabine, or bortezomib, or with immunosuppressive agents, such as cyclosporine. As in warm IgG-mediated autoimmune hemolysis, it may be difficult to find compatible blood for transfusion. RBCs should be transfused through an in-line blood warmer.

Berentsen S. How I treat cold agglutinin disease. Blood. 2021;137:1295. [PMID: 33512410]
Jäger U et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the First International Consensus Meeting. Blood Rev. 2020;41:100648. [PMID: 31839434]

APLASTIC ANEMIA

ESSENTIALS OF DIAGNOSIS

- Pancytopenia.
- No abnormal hematopoietic cells seen in blood or bone marrow.
- Hypocellular bone marrow.

General Considerations

Aplastic anemia is a condition of bone marrow failure that arises from suppression of, or injury to, the hematopoietic stem cell. The bone marrow becomes hypoplastic, fails to produce mature blood cells, and pancytopenia develops.

There are a number of causes of aplastic anemia (Table 13–10). Direct hematopoietic stem cell injury may be caused by radiation, chemotherapy, toxins, or pharmacologic agents. SLE may rarely cause suppression of the hematopoietic stem cell by an IgG autoantibody directed against it. However, the most common pathogenesis of aplastic anemia appears to be autoimmune suppression of

Table 13–10. Causes of aplastic anemia.

Autoimmune: idiopathic, SLE
Congenital: defects in telomere length maintenance or DNA repair (dyskeratosis congenita, Fanconi anemia, etc)
Chemotherapy, radiotherapy
Toxins: benzene, toluene, insecticides
Medications: chloramphenicol, gold salts, sulfonamides, phenytoin, carbamazepine, quinacrine, tolbutamide
Post-viral hepatitis (viral agent known or unknown)
Non-hepatitis viruses (EBV, parvovirus, CMV, echovirus 3, others)
Pregnancy
Paroxysmal nocturnal hemoglobinuria
Malignancy: large granular lymphocytic leukemia (T-LGL)

CMV, cytomegalovirus; EBV, Epstein-Barr virus.

hematopoiesis by a T-cell-mediated cellular mechanism, so-called idiopathic aplastic anemia. In some cases of idiopathic aplastic anemia, defects in maintenance of the hematopoietic stem cell telomere length (eg, dyskeratosis congenita) or in DNA repair pathways (eg, Fanconi anemia) have been identified and are likely linked to both the initiation of bone marrow failure and the propensity to later progress to myelodysplasia, PNH, or AML. Complex detrimental immune responses to viruses can also cause aplastic anemia.

Clinical Findings

A. Symptoms and Signs

Patients come to medical attention because of the consequences of bone marrow failure. Anemia leads to symptoms of weakness and fatigue, neutropenia causes vulnerability to bacterial or fungal infections, and thrombocytopenia results in mucosal and skin bleeding. Physical examination may reveal signs of pallor, purpura, and petechiae. Other abnormalities such as hepatosplenomegaly, lymphadenopathy, or bone tenderness should *not* be present, and their presence should lead to questioning the diagnosis.

B. Laboratory Findings

The hallmark of aplastic anemia is pancytopenia (neutropenia, anemia, and thrombocytopenia). However, early in the evolution of aplastic anemia, only one or two cell lines may be reduced.

Anemia may be severe and is always associated with reticulocytopenia. RBC morphology is unremarkable, but there may be mild macrocytosis (increased MCV). Neutrophils and platelets are reduced in number, and no immature or abnormal forms are seen on the blood smear. The bone marrow aspirate and the bone marrow biopsy appear hypocellular, with only scant amounts of morphologically normal hematopoietic progenitors. The prior dictum that the bone marrow karyotype should be normal (or germline if normal variant) has evolved and some clonal abnormalities or other genetic aberrations may be present even in the setting of idiopathic aplastic anemia.

Differential Diagnosis

Aplastic anemia must be differentiated from other causes of pancytopenia (Table 13–11). Hypocellular forms of myelodysplasia or acute leukemia may occasionally be confused with aplastic anemia. These are differentiated by the presence of cellular morphologic abnormalities, increased percentage of blasts, or abnormal karyotype in bone marrow cells typical of MDS or acute leukemia. Hairy cell leukemia has been misdiagnosed as aplastic anemia and should be recognized by the presence of splenomegaly and by abnormal "hairy" lymphoid cells in a hypocellular bone marrow biopsy. Pancytopenia with a normocellular bone marrow may be due to SLE, disseminated infection, hypersplenism, nutritional (eg, vitamin B_{12} or folate) deficiency, or myelodysplasia. Isolated thrombocytopenia may occur early as aplastic anemia develops and may be confused with immune thrombocytopenia.

Table 13–11. Causes of pancytopenia.

Bone marrow disorders
Aplastic anemia
Myelodysplasia
Acute leukemia
Chronic idiopathic myelofibrosis
Infiltrative disease: lymphoma, myeloma, carcinoma, hairy cell leukemia, etc
Non–bone marrow disorders
Hypersplenism (with or without portal hypertension)
SLE
Infection: tuberculosis, HIV, leishmaniasis, brucellosis, CMV, parvovirus B19
Nutritional deficiency (megaloblastic anemia)
Medications
Cytotoxic chemotherapy
Ionizing radiation

CMV, cytomegalovirus.

Treatment

Mild cases of idiopathic aplastic anemia may be treated with supportive care, including erythropoietic (epoetin or darbepoetin) or myeloid (filgrastim or sargramostim or biosimilars) growth factors, or both. RBC transfusions and platelet transfusions are given as necessary, and antibiotics are used to treat or prevent infections.

Severe aplastic anemia is defined by a neutrophil count of less than 500/mcL (0.5×10^9/L), platelets less than 20,000/mcL (20×10^9/L), reticulocytes less than 1%, and bone marrow cellularity less than 20%. The treatment of choice for young adults (under age 40 years) who have an HLA-matched sibling is allogeneic bone marrow transplantation. Children or young adults may also benefit from allogeneic bone marrow transplantation using an unrelated donor. Because of the increased risks associated with unrelated donor allogeneic bone marrow transplantation compared to sibling donors, this treatment is usually reserved for patients who have not responded to immunosuppressive therapy.

For adults over age 40 years or those without HLA-matched hematopoietic stem cell donors, the treatment of choice for severe idiopathic aplastic anemia is immunosuppression and hematopoietic stimulation with equine antithymocyte globulin (ATG) plus cyclosporine and eltrombopag (the thrombopoietin mimetic) (response rates approaching 90%). Equine ATG is given in the hospital in conjunction with transfusion and antibiotic support. A proven regimen is equine ATG 40 mg/kg/day intravenously for 4 days in combination with cyclosporine, 6 mg/kg orally twice daily, and eltrombopag, 150 mg orally daily. Equine ATG is superior to rabbit ATG, resulting in a higher response rate and better survival. ATG should be used in combination with corticosteroids (prednisone or methylprednisolone 1–2 mg/kg/day orally for 1 week, followed by a taper over 2 weeks) to avoid ATG infusion reactions and serum sickness. Responses usually occur in 1–3 months and are usually only partial, but the blood counts rise high enough to give patients a safe and transfusion-free life. The full benefit of

immunosuppression is generally assessed at 4 months post-equine ATG. Cyclosporine and eltrombopag are maintained at full doses for 6 months and then stopped in responding patients. Androgens (such as fluoxymesterone 10–20 mg/day orally in divided doses or danazol 200 mg orally twice daily) have been widely used in the past, with a low response rate, and may be considered in mild cases.

Course & Prognosis

Patients with severe aplastic anemia have a rapidly fatal illness if left untreated. Allogeneic bone marrow transplant from an HLA-matched sibling donor produces survival rates of over 80% in recipients under 20 years old and of about 65–70% in those 20 to 50 years old. Respective survival rates drop by 10–15% when the donor is HLA-matched but unrelated. Equine ATG-cyclosporine immunosuppressive treatment leads to a response in approximately 70% of patients (including those with hepatitis virus–associated aplastic anemia) and in up to 90% of patients with the addition of eltrombopag. Up to one-third of patients will relapse with aplastic anemia after ATG-based therapy. Clonal hematologic disorders, such as PNH, AML, or myelodysplasia, may develop in one-quarter of patients treated with immunosuppressive therapy after 10 years of follow-up. Factors that predict response to ATG-cyclosporine therapy are patient's age, reticulocyte count, lymphocyte count, and age-adjusted telomere length of leukocytes at the time of diagnosis.

When to Refer

All patients should be referred to a hematologist.

When to Admit

Admission is necessary for treatment of neutropenic infection, the administration of ATG, or allogeneic bone marrow transplantation.

DeZern AE et al. Approach to the diagnosis of aplastic anemia. Blood Adv. 2021;5:2660. [PMID: 34156438]
Georges GE et al. Severe aplastic anemia: allogeneic bone marrow transplantation as first line treatment. Blood Adv. 2020;2:2020. [PMID: 30108110]
Marsh JCW et al. The case for upfront HLA-matched unrelated donor hematopoietic stem cell transplantation as a curative option for adult acquired severe aplastic anemia. Biol Blood Marrow Transplant. 2019;25:e277. [PMID: 31129354]
Zhu Y et al. Allo-HSCT compared with immunosuppressive therapy for acquired aplastic anemia: a system review and meta-analysis. BMC Immunol. 2020;2:10. [PMID: 32138642]

NEUTROPENIA

ESSENTIALS OF DIAGNOSIS

- Neutrophils < 1800/mcL (1.8×10^9/L).
- Severe if neutrophils < 500/mcL (0.5×10^9/L).

General Considerations

Neutropenia is present when the absolute neutrophil count is less than 1800/mcL (1.8×10^9/L), although Black, Asian, and other persons in specific ethnic groups may have normal neutrophil counts as low as 800–1200/mcL (1.2×10^9/L) or even less. The neutropenic patient is increasingly vulnerable to infection by gram-positive and gram-negative bacteria and by fungi. The risk of infection is related to the severity of neutropenia. The risk of serious infection rises sharply with neutrophil counts below 500/mcL (0.5×10^9/L), and a high risk of infection within days occurs with neutrophil counts below 100/mcL (0.1×10^9/L) ("profound neutropenia"). The classification of neutropenic syndromes is unsatisfactory as the pathophysiology and natural history of different syndromes overlap. Patients with "chronic benign neutropenia" are free of infection despite very low stable neutrophil counts; they respond adequately to infections and inflammatory stimuli with an appropriate neutrophil release from the bone marrow. In contrast, the neutrophil count of patients with cyclic neutropenia periodically oscillates (usually in 21-day cycles) between normal and low, with infections occurring during the nadirs. Congenital neutropenia is lifelong neutropenia punctuated with bouts of infection.

A variety of bone marrow disorders and non-marrow conditions may cause neutropenia (Table 13–12). All of the causes of aplastic anemia (Table 13–10) and pancytopenia (Table 13–11) may cause neutropenia. The new onset of an isolated neutropenia is most often due to an idiosyncratic reaction to a medication, and agranulocytosis (complete absence of neutrophils in the peripheral blood) is almost always due to a drug reaction. In these cases, examination of the bone marrow shows an almost complete absence of granulocyte precursors with other cell lines undisturbed. Neutropenia in the presence of a normal bone marrow may

Table 13–12. Causes of neutropenia.

Bone marrow disorders
Congenital
Dyskeratosis congenita
Fanconi anemia
Cyclic neutropenia
Congenital neutropenia
Hairy cell leukemia
Large granular lymphoproliferative disorder
Myelodysplasia
Non–bone marrow disorders
Medications: antiretroviral medications, cephalosporins, chlorpromazine, chlorpropamide, cimetidine, methimazole, myelosuppressive cytotoxic chemotherapy, penicillin, phenytoin, procainamide, rituximab, sulfonamides
Aplastic anemia
Benign chronic neutropenia
Pure WBC aplasia
Hypersplenism
Sepsis
Other immune
Autoimmune (idiopathic)
Felty syndrome
SLE
HIV infection

be due to immunologic peripheral destruction (autoimmune neutropenia), sepsis, or hypersplenism. The presence in the serum of antineutrophil antibodies supports the diagnosis of autoimmune neutropenia but does not prove this as the pathophysiologic reason for neutropenia. **Felty syndrome** is an immune neutropenia associated with seropositive nodular rheumatoid arthritis and splenomegaly. Severe neutropenia may be associated with clonal disorders of T lymphocytes, often with the morphology of large granular lymphocytes, referred to as CD3-positive T-cell large granular lymphoproliferative disorder. Isolated neutropenia is an uncommon presentation of hairy cell leukemia or MDS. By its nature, myelosuppressive cytotoxic chemotherapy causes neutropenia in a predictable manner.

Clinical Findings

Neutropenia results in stomatitis and in infections due to gram-positive or gram-negative aerobic bacteria or to fungi such as *Candida* or *Aspergillus*. The most common infectious syndromes are sinusitis, cellulitis, pneumonia, septicemia, and neutropenic fever of unknown origin. Fever in neutropenic patients should always be initially assumed to be of infectious origin until proven otherwise (Chapter 30).

Treatment

Treatment of neutropenia depends on its cause. Potential causative medications should be discontinued. Myeloid growth factors (filgrastim or sargramostim or biosimilar myeloid growth factors) help facilitate neutrophil recovery after offending medications are stopped. Chronic myeloid growth factor administration (daily or every other day) is effective at dampening the neutropenia seen in cyclic or congenital neutropenia. When Felty syndrome leads to repeated bacterial infections, splenectomy has been the treatment of choice, but sustained use of myeloid growth factors is effective and provides a nonsurgical alternative. Patients with autoimmune neutropenia respond briefly to immunosuppression with corticosteroids and are best managed with intermittent doses of myeloid growth factors. The neutropenia associated with large granular lymphoproliferative disorder may respond to therapy with oral methotrexate, cyclophosphamide, or cyclosporine.

Fevers during neutropenia should be considered as infectious until proven otherwise. Febrile neutropenia is a life-threatening circumstance. Enteric gram-negative bacteria are of primary concern and often empirically treated with fluoroquinolones or third- or fourth-generation cephalosporins (see Infections in the Immunocompromised Patient, Chapter 30). For protracted neutropenia, fungal infections are problematic and empiric coverage with azoles (fluconazole for yeast and voriconazole, itraconazole, posaconazole, or isavuconazole for molds) or echinocandins is recommended. The neutropenia following myelosuppressive chemotherapy is predictable and is partially ameliorated by the use of myeloid growth factors. For patients with acute leukemia undergoing intense chemotherapy or patients with solid cancer undergoing high-dose chemotherapy, the prophylactic use of antimicrobial agents and myeloid growth factors is recommended.

When to Refer

Refer to a hematologist if neutrophils are persistently and unexplainably less than 1000/mcL (1.0×10^9/L).

When to Admit

Neutropenia by itself is not an indication for hospitalization. However, many patients with severe neutropenia may have a serious underlying disease that may require inpatient treatment. Most patients with febrile neutropenia require hospitalization to treat infection.

Abdel-Azim H et al. Strategies to generate functionally normal neutrophils to reduce infection and infection-related mortality in cancer chemotherapy. Pharmacol Ther. 2019;204:107403. [PMID: 31470030]
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LEUKEMIAS & OTHER MYELOPROLIFERATIVE NEOPLASMS

Myeloproliferative disorders are due to acquired clonal abnormalities of the hematopoietic stem cell. Since the stem cell gives rise to myeloid, erythroid, and platelet cells, qualitative and quantitative changes are seen in all of these cell lines. Classically, the myeloproliferative disorders produce characteristic syndromes with well-defined clinical and laboratory features (Tables 13–13 and 13–14). However, these disorders are grouped together because they may evolve from one into another and because hybrid disorders are commonly seen. All of the myeloproliferative disorders may progress to AML.

Table 13–13. World Health Organization classification of myeloproliferative disorders (modified).

Myeloproliferative neoplasms
Chronic myeloid leukemia, *BCR-ABL1*–positive
Chronic neutrophilic leukemia
Polycythemia vera
Primary myelofibrosis (PMF)
Essential thrombocythemia
Chronic eosinophilic leukemia, not otherwise specified (NOS)
Myeloproliferative neoplasm, unclassifiable
Mastocytosis
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Myelodysplastic syndromes
Acute myeloid leukemia and related neoplasms
Acute myeloid leukemia with recurrent genetic abnormalities
Acute myeloid leukemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, NOS
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Acute leukemias of ambiguous lineage
B lymphoblastic leukemia/lymphoma
T lymphoblastic leukemia/lymphoma

Table 13–14. Laboratory features of myeloproliferative neoplasms.

	White Count	Hematocrit	Platelet Count	RBC Morphology
Polycythemia vera	N or ↑	↑↑	N or ↑	N
Essential thrombocytosis	N or ↑	N	↑↑	N
Primary myelofibrosis	N or ↓ or ↑	↓	↓ or N or ↑	Abn
Chronic myeloid leukemia	↑↑	N or ↓	N or ↑ or ↓	N

Abn, abnormal; N, normal.

The Philadelphia chromosome seen in chronic myeloid leukemia (CML) was the first recurrent cytogenetic abnormality to be described in a human malignancy. Since that time, there has been tremendous progress in elucidating the genetic nature of these disorders, with identification of mutations in *JAK2, MPL, CALR, CSF3R*, and other genes.

Masarova L et al. The rationale for immunotherapy in myeloproliferative neoplasms. Curr Hematol Malig Rep. 2019;14:310. [PMID: 31228096]
Schwede M et al. Diagnosis and management of neutrophilic myeloid neoplasms. Clin Adv Hematol Oncol. 2021;19:450. [PMID: 34236344]

POLYCYTHEMIA VERA

ESSENTIALS OF DIAGNOSIS

- *JAK2 (V617F)* mutation.
- Splenomegaly.
- Normal arterial oxygen saturation.
- Usually elevated white blood count and platelet count.

General Considerations

Polycythemia vera is an acquired myeloproliferative disorder that causes overproduction of all three hematopoietic cell lines, most prominently the RBCs. Erythroid production is independent of erythropoietin, and the serum erythropoietin level is low. True erythrocytosis, with an elevated RBC mass, should be distinguished from spurious erythrocytosis caused by a constricted plasma volume.

A mutation in exon 14 of *JAK2 (V617F)*, a signaling molecule, has been demonstrated in 95% of cases. Additional *JAK2* mutations have been identified (exon 12) and suggest that *JAK2* is involved in the pathogenesis of this disease and is a therapeutic target.

Clinical Findings

A. Symptoms and Signs

Headache, dizziness, tinnitus, blurred vision, and fatigue are common complaints related to expanded blood volume and increased blood viscosity. Generalized pruritus, especially following a warm shower or bath, is related to histamine release from the basophilia. Epistaxis is related to engorgement of mucosal blood vessels in combination with abnormal hemostasis. Sixty percent of patients are men, and the median age at presentation is 60 years. Polycythemia rarely occurs in persons under age 40 years.

Physical examination reveals plethora and engorged retinal veins. The spleen is palpable in 75% of cases but is nearly always enlarged when imaged. Thrombosis is the most common complication of polycythemia vera and the major cause of morbidity and death in this disorder. Thrombosis appears to be related both to increased blood viscosity and abnormal platelet function. Uncontrolled polycythemia leads to a very high incidence of thrombotic complications of surgery, and elective surgery should be deferred until the condition has been treated. Paradoxically, in addition to thrombosis, increased bleeding can occur. There is also a high incidence of peptic ulcer disease.

B. Laboratory Findings

According to the WHO 2016 criteria, the hallmark of polycythemia vera is a hematocrit (at sea level) that exceeds 49% in males or 48% in females. RBC morphology is normal (Table 13–14). The white blood count is usually elevated to 10,000–20,000/mcL ($10–20 \times 10^9$/L), and the platelet count is variably increased, sometimes to counts exceeding 1,000,000/mcL (1000×10^9/L). Platelet morphology is usually normal. WBCs are usually normal, but basophilia and eosinophilia are frequently present. Erythropoietin is suppressed and serum levels, usually low. The diagnosis should be confirmed with *JAK2* mutation screening. The absence of a mutation in either exon 14 (most common) or 12 should lead the clinician to question the diagnosis.

The bone marrow is hypercellular, with hyperplasia of all hematopoietic elements, but bone marrow examination is not necessary to establish the diagnosis. Iron stores are usually absent from the bone marrow, having been transferred to the increased circulating RBC mass. Iron deficiency may also result from chronic GI blood loss. Bleeding may lower the hematocrit to the normal range (or lower), creating diagnostic confusion, and may lead to a situation with significant microcytosis yet a normal hematocrit.

Vitamin B_{12} levels are strikingly elevated because of increased levels of transcobalamin III (secreted by WBCs). Overproduction of uric acid may lead to hyperuricemia.

Although RBC morphology is usually normal at presentation, microcytosis, hypochromia, and poikilocytosis

may result from iron deficiency following treatment by phlebotomy. Progressive hypersplenism may also lead to elliptocytosis (eg, with RBCs the size and shape of those in hereditary elliptocytosis).

Differential Diagnosis

Spurious polycythemia, in which an elevated hematocrit is due to contracted plasma volume rather than increased RBC mass, may be related to diuretic use or may occur without obvious cause.

A secondary cause of polycythemia should be suspected if splenomegaly is absent and the high hematocrit is not accompanied by increases in other cell lines. Secondary causes of polycythemia include hypoxia and smoking; carboxyhemoglobin levels may be elevated in smokers (Table 13–15). A renal CT scan or sonogram may be considered to look for an erythropoietin-secreting cyst or tumor. A positive family history should lead to investigation for a congenital high-oxygen-affinity hemoglobin. An absence of a mutation in *JAK2* suggests a different diagnosis. However, *JAK2* mutations are also commonly found in other myeloproliferative disorders, essential thrombocytosis, and myelofibrosis.

Polycythemia vera should be differentiated from other myeloproliferative disorders (Table 13–14). Marked elevation of the white blood count (above 30,000/mcL [30 × 10^9/L]) suggests CML. Abnormal RBC morphology and nucleated RBCs in the peripheral blood are seen in myelofibrosis. Essential thrombocytosis is suggested when the platelet count is strikingly elevated.

Treatment

The treatment of choice is phlebotomy. One unit of blood (approximately 500 mL) is removed weekly until the hematocrit is less than 45%; the hematocrit is maintained at less than 45% by repeated phlebotomy as necessary. Patients for whom phlebotomy is problematic (because of poor venous access or logistical reasons) may be managed primarily with hydroxyurea. Because repeated phlebotomy intentionally produces iron deficiency, the requirement for phlebotomy should gradually decrease. It is important to avoid medicinal iron supplementation, as this can thwart the goals of a phlebotomy program. A diet low in iron is not necessary but will increase the intervals between phlebotomies. Maintaining the hematocrit at normal levels has been shown to decrease the incidence of thrombotic complications.

Occasionally, myelosuppressive therapy is indicated. Indications include a high phlebotomy requirement, thrombocytosis, and intractable pruritus. There is evidence that reduction of the platelet count to less than 600,000/mcL (600 × 10^9/L) will reduce the risk of thrombotic complications. Hydroxyurea is widely used when myelosuppressive therapy is indicated. The usual dose is 500–1500 mg/day orally, adjusted to keep platelets less than 500,000/mcL (500 × 10^9/L) without reducing the neutrophil count to less than 2000/mcL (2.0 × 10^9/L). Alkylating agents, such as busulfan and pipobroman, can be used for refractory cases but have been shown to increase the risk of conversion of this disease to acute leukemia and thus should be used with caution.

A randomized phase 3 trial comparing ropeginterferon alfa-2b, a novel interferon, to hydroxyurea demonstrated improved disease control rates in patients presenting without splenomegaly with 53% vs 38% of patients achieving a complete hematologic response and with improved disease burden at 3 years' follow-up. Toxicity included abnormal liver biochemical tests in the ropeginterferon alfa-2b group, and leukopenia and thrombocytopenia in the standard therapy group, with serious adverse events occurring in 2% in the former and 4% in the latter group. As a result, ropeginterferon alfa-2b was approved by the European Medicines Agency as first-line therapy for patients without symptomatic splenomegaly.

Low-dose aspirin (75–81 mg/day orally) has been shown to reduce the risk of thrombosis without excessive bleeding and should be part of therapy for all patients without contraindications to aspirin. Aspirin should be used with caution in patients with extreme thrombocytosis due to the likelihood of acquired von Willebrand disease. Allopurinol 300 mg orally daily may be indicated for hyperuricemia. Antihistamine therapy with diphenhydramine or other H_1-blockers and, rarely, SSRIs are used to manage pruritus.

Table 13–15. Causes of polycythemia.

Spurious polycythemia
Secondary polycythemia
Hypoxia: cardiac disease, pulmonary disease, high altitude
Carboxyhemoglobin: smoking
Erythropoietin-secreting tumors, eg, kidney lesions (rare)
Abnormal hemoglobins (rare)
Polycythemia vera

Prognosis

Polycythemia is an indolent disease with median survival of over 15 years. The major cause of morbidity and mortality is arterial thrombosis. Over time, polycythemia vera may convert to myelofibrosis. In approximately 5% of cases, the disorder progresses to AML, which is usually refractory to therapy.

When to Refer

Patients with polycythemia vera should be referred to a hematologist.

When to Admit

Inpatient care is rarely required.

Barbui T et al. The 2016 revision of WHO classification of myeloproliferative neoplasms: clinical and molecular advances. Blood Rev. 2016;30:453. [PMID: 27341755]

Gangat N et al. *JAK2* unmutated erythrocytosis: current diagnostic approach and therapeutic views. Leukemia. 2021;35:2166. [PMID: 34021251]

Gisslinger H et al; PROUD-PV Study Group. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematol. 2020;7:e196. [PMID: 32014125]

Ronner L et al. Improving the investigative approach to polycythaemia vera: a critical assessment of current evidence and vision for the future. Lancet Haematol. 2021;8:e605. [PMID: 34329580]
Tefferi A et al. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95:1599. [PMID: 32974939]

ESSENTIAL THROMBOCYTOSIS

ESSENTIALS OF DIAGNOSIS

- Elevated platelet count in absence of other causes.
- Normal RBC mass.
- Absence of *bcr/abl* gene (Philadelphia chromosome).

General Considerations

Essential thrombocytosis is an uncommon myeloproliferative disorder in which marked proliferation of the megakaryocytes in the bone marrow leads to elevation of the platelet count. As with polycythemia vera, the finding of a high frequency of mutations of *JAK2* and others in these patients has advanced the understanding of this disorder.

Clinical Findings

A. Symptoms and Signs

The median age at presentation is 50–60 years, and there is a slightly increased incidence in women. The disorder is often suspected when an elevated platelet count is found. Less frequently, the first sign is thrombosis, which is the most common clinical problem. The risk of thrombosis rises with age. Venous thromboses may occur in unusual sites such as the mesenteric, hepatic, or portal vein. Some patients experience erythromelalgia, painful burning of the hands accompanied by erythema; this symptom is reliably relieved by aspirin. Bleeding, typically mucosal, is less common and is related to a concomitant qualitative platelet defect. Splenomegaly is present in at least 25% of patients.

B. Laboratory Findings

An elevated platelet count is the hallmark of this disorder and may be over 2,000,000/mcL (2000×10^9/L) (Table 13–14). The WBC count is often mildly elevated, usually not above 30,000/mcL (30×10^9/L), but with some immature myeloid forms. The hematocrit is normal. The peripheral blood smear reveals large platelets, but giant degranulated forms seen in myelofibrosis are not observed. RBC morphology is normal.

The bone marrow shows increased numbers of megakaryocytes but no other morphologic abnormalities. The peripheral blood should be tested for the *bcr/abl* fusion gene (Philadelphia chromosome) since it can differentiate CML, where it is present, from essential thrombocytosis, where it is absent.

Differential Diagnosis

Essential thrombocytosis must be distinguished from secondary causes of an elevated platelet count. In reactive thrombocytosis, the platelet count seldom exceeds 1,000,000/mcL (1000×10^9/L). Inflammatory disorders such as rheumatoid arthritis and ulcerative colitis cause significant elevations of the platelet count, as may chronic infection. The thrombocytosis of iron deficiency is observed only when anemia is significant. The platelet count is temporarily elevated after a splenectomy. *JAK2* mutations are found in over 50% of cases. *MPL* and *CALR* mutations frequently occur in patients with *JAK2*-negative essential thrombocytosis.

Regarding other myeloproliferative disorders, the lack of erythrocytosis distinguishes it from polycythemia vera. Unlike myelofibrosis, RBC morphology is normal, nucleated RBCs are absent, and giant degranulated platelets are not seen. In CML, the Philadelphia chromosome (or *bcr/abl* by molecular testing) establishes the diagnosis.

Treatment

Patients are considered at high risk for thrombosis if they are older than 60 years, have a *JAK2* mutation, and have a previous history of thrombosis. They also have a higher risk for bleeding. The risk of thrombosis can be reduced by control of the platelet count, which should be kept under 500,000/mcL (500×10^9/L). The treatment of choice is oral hydroxyurea in a dose of 500–1000 mg/day. In rare cases in which hydroxyurea is not well tolerated because of anemia, low doses of anagrelide, 1–2 mg/day orally, may be added. Higher doses of anagrelide can be complicated by headache, peripheral edema, and heart failure. Pegylated interferon alfa-2 can induce significant hematologic responses and can potentially target the malignant clone in *CALR*-mutant cases. Strict control of coexistent cardiovascular risk factors is mandatory for all patients.

Vasomotor symptoms such as erythromelalgia and paresthesias respond rapidly to aspirin. Historically, low-dose aspirin (81 mg/day orally) has been used to reduce the risk of thrombotic complications in low-risk patients, but a recent study found that once daily dosing is not as effective as an every 12-hour regimen. In the unusual event of severe bleeding, the platelet count can be lowered rapidly with plateletpheresis. In cases of marked thrombocytosis (greater than or equal to 1,000,000/mcL [1000×10^9/L]) or of any evidence of bleeding, acquired von Willebrand syndrome must be excluded before starting low-dose aspirin.

Course & Prognosis

Essential thrombocytosis is an indolent disorder that allows long-term survival. Average survival is longer than 15 years from diagnosis, and the survival of patients younger than age 50 years does not appear different from matched controls. The major source of morbidity—thrombosis—can be reduced by appropriate platelet control. Late in the disease course, the bone marrow may become fibrotic, and massive splenomegaly may occur,

sometimes with splenic infarction. There is a 10–15% risk of progression to myelofibrosis after 15 years, and a 1–5% risk of transformation to acute leukemia over 20 years.

When to Refer

Patients with essential thrombocytosis should be referred to a hematologist.

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Rocca B et al. A randomized double-blind trial of 3 aspirin regimens to optimize antiplatelet therapy in essential thrombocythemia. Blood. 2020;136:171. [PMID: 32266380]

PRIMARY MYELOFIBROSIS

ESSENTIALS OF DIAGNOSIS

- Striking splenomegaly.
- Teardrop poikilocytosis on peripheral smear.
- Leukoerythroblastic blood picture; giant abnormal platelets.
- Initially hypercellular, then hypocellular bone marrow with reticulin or collagen fibrosis.

General Considerations

Primary myelofibrosis is a myeloproliferative disorder characterized by clonal hematopoiesis that is often but not always accompanied by *JAK2*, *CALR*, or *MPL* mutations; bone marrow fibrosis; anemia; splenomegaly; and a leukoerythroblastic peripheral blood picture with teardrop poikilocytosis. Myelofibrosis can also occur as a secondary process following the other myeloproliferative disorders (eg, polycythemia vera, essential thrombocytosis). It is believed that fibrosis occurs in response to increased secretion of platelet-derived growth factor (PDGF) and possibly other cytokines. In response to bone marrow fibrosis, extramedullary hematopoiesis takes place in the liver, spleen, and lymph nodes. In these sites, mesenchymal cells responsible for fetal hematopoiesis can be reactivated. According to the 2016 WHO classification, "prefibrotic" primary myelofibrosis is distinguished from "overtly fibrotic" primary myelofibrosis; the former might mimic essential thrombocytosis in its presentation, and it is prognostically relevant to distinguish the two.

Clinical Findings

A. Symptoms and Signs

Primary myelofibrosis develops in adults over age 50 years and is usually insidious in onset. Patients most commonly present with fatigue due to anemia or abdominal fullness related to splenomegaly. Uncommon presentations include bleeding and bone pain. On examination, splenomegaly is almost invariably present and is commonly massive. The liver is enlarged in more than 50% of cases.

Later in the course of the disease, progressive bone marrow failure takes place as it becomes increasingly more fibrotic. Progressive thrombocytopenia leads to bleeding. The spleen continues to enlarge, which leads to early satiety. Painful episodes of splenic infarction may occur. The patient becomes cachectic and may experience severe bone pain, especially in the upper legs. Hematopoiesis in the liver leads to portal hypertension with ascites and esophageal varices, and occasionally myelopoiesis in the epidural space causes transverse myelitis.

B. Laboratory Findings

Patients are almost invariably anemic at presentation. The white blood count is variable—either low, normal, or elevated—and may be increased to 50,000/mcL (50×10^9/L). The platelet count is variable. The peripheral blood smear is dramatic, with significant poikilocytosis and numerous teardrop forms in the RBC line. Nucleated RBCs are present, and the myeloid series is shifted, with immature forms including a small percentage of promyelocytes or myeloblasts. Platelet morphology may be bizarre, and giant degranulated platelet forms (megakaryocyte fragments) may be seen. The triad of teardrop poikilocytosis, leukoerythroblastic blood, and giant abnormal platelets is highly suggestive of myelofibrosis.

The bone marrow usually cannot be aspirated (dry tap), though early in the course of the disease, biopsy shows it to be hypercellular, with a marked increase in megakaryocytes. Fibrosis at this stage is detected by a silver stain demonstrating increased reticulin fibers. Later, biopsy reveals more severe fibrosis, with eventual replacement of hematopoietic precursors by collagen. There is no characteristic chromosomal abnormality. *JAK2* is mutated in ~65% of cases, and *MPL* and *CALR* are mutated in the majority of the remaining cases; 10% of cases are "triple-negative."

Differential Diagnosis

A leukoerythroblastic blood picture from other causes may be seen in response to severe infection, inflammation, or infiltrative bone marrow processes. However, teardrop poikilocytosis and giant abnormal platelet forms will not be present. Bone marrow fibrosis may be seen in metastatic carcinoma, Hodgkin lymphoma, and hairy cell leukemia. These disorders are diagnosed by characteristic morphology of involved tissues.

Of the other myeloproliferative disorders, CML is diagnosed when there is marked leukocytosis, normal RBC morphology, and the presence of the *bcr/abl* fusion gene. Polycythemia vera is characterized by an elevated hematocrit. Essential thrombocytosis shows predominant platelet count elevations.

Treatment

Observation with supportive care is a reasonable treatment strategy for asymptomatic patients with low risk or an intermediate risk, especially in the absence of high-risk mutations.

Anemic patients are supported with transfusion. Anemia can also be controlled with androgens, prednisone, thalidomide, or lenalidomide. First-line therapy for myelofibrosis-associated splenomegaly is hydroxyurea 500–1000 mg/day orally, which is effective in reducing spleen size by half in approximately 40% of patients. Both thalidomide and lenalidomide may improve splenomegaly and thrombocytopenia in some patients. Splenectomy is not routinely performed but is indicated for medication-refractory splenic enlargement causing recurrent painful episodes, severe thrombocytopenia, or an unacceptable transfusion requirement. Perioperative complications can occur in 28% of patients and include infections, abdominal vein thrombosis, and bleeding. Radiation therapy has a role for painful sites of extramedullary hematopoiesis, pulmonary hypertension, or severe bone pain. Transjugular intrahepatic portosystemic shunt might also be considered to alleviate symptoms of portal hypertension.

Certain patients with intermediate-risk and those with high- or very high-risk disease should be considered for allogeneic stem cell transplant, which is currently the only potentially curative treatment modality for primary myelofibrosis. Nontransplant candidates may be treated with JAK2 inhibitors or immunomodulatory agents for symptom control. Ruxolitinib, an FDA-approved JAK2 inhibitor, results in reduction of spleen size and improvement of constitutional symptoms but does not induce complete clinical or cytogenetic remissions or significantly affect the *JAK2/CALR/MPL* mutant allele burden. Moreover, ruxolitinib can exacerbate cytopenias. Another FDA-approved selective JAK2 inhibitor, fedratinib, can lead to sustained reduction in spleen size and improvement in disease-associated symptoms for patients with advanced- stage myelofibrosis. However, it carries a significant risk of serious and fatal encephalopathy, including Wernicke encephalopathy, and providers should regularly assess thiamine levels in all patients. The immunomodulatory medications lenalidomide and pomalidomide result in control of anemia in 25% and thrombocytopenia in ~58% of cases, without significant reduction in splenic size.

Course & Prognosis

The median survival from time of diagnosis is approximately 5 years. Therapies with biologic agents and the application of reduced-intensity allogeneic stem cell transplantation appear to offer the possibility of improving the outcome for many patients. End-stage myelofibrosis is characterized by generalized asthenia, liver failure, and bleeding from thrombocytopenia, with some cases terminating in AML. Two new prognostic systems for primary myelofibrosis have recently been introduced: GIPSS (genetically inspired prognostic scoring system) and MIPSS70+ version 2.0 (MIPSSv2; genetic variant- (formerly, mutation-) and karyotype-enhanced international prognostic scoring system). GIPSS is based exclusively on mutations and karyotype. MIPSSv2 includes, in addition to genetic and karyotypic variants, clinical risk factors. Patients with certain pathogenic variants including *ASXL1* and *SRSF2* have an adverse prognosis regardless of clinical features. By contrast, patients with type 1/like *CALR* variants, compared to their counterparts with other driver mutations, experience significantly better survival.

When to Refer

Patients in whom myelofibrosis is suspected should be referred to a hematologist.

When to Admit

Admission is not usually necessary.

Rumi E et al. The genetic basis of primary myelofibrosis and its clinical relevance. Int J Mol Sci. 2020;21:8885. [PMID: 33255170]

Talpaz M et al. Fedratinib, a newly approved treatment for patients with myeloproliferative neoplasm-associated myelofibrosis. Leukemia. 2021;35:1. [PMID: 32647323]

Tefferi A. Primary myelofibrosis: 2021 update on diagnosis, risk-stratification and management. Am J Hematol. 2021;96:145. [PMID: 33197049]

CHRONIC MYELOID LEUKEMIA

ESSENTIALS OF DIAGNOSIS

- Elevated WBC count.
- Markedly left-shifted myeloid series but with a low percentage of promyelocytes and blasts.
- Presence of *bcr/abl* gene (Philadelphia chromosome).

General Considerations

CML is a myeloproliferative disorder characterized by overproduction of myeloid cells. These myeloid cells continue to differentiate and circulate in increased numbers in the peripheral blood.

CML is characterized by a specific chromosomal abnormality and a specific molecular abnormality. The **Philadelphia chromosome** is a reciprocal translocation between the long arms of chromosomes 9 and 22. The fusion gene *bcr/abl* produces a novel protein that possesses tyrosine kinase activity. This disorder is the first recognized example of tyrosine kinase "addiction" by cancer cells.

Early CML ("chronic phase") does not behave like a malignant disease. Normal bone marrow function is retained, WBCs differentiate, and despite some qualitative abnormalities, the neutrophils combat infections normally. However, untreated CML is inherently unstable, and without treatment, the disease progresses to an "accelerated" phase and then an "acute blast" phase, which is morphologically indistinguishable from acute leukemia.

Clinical Findings

A. Symptoms and Signs

CML is a disorder of middle age (median age at presentation is 55 years). Patients usually complain of fatigue, night

sweats, and low-grade fevers related to the hypermetabolic state caused by overproduction of WBCs. Patients may also complain of abdominal fullness related to splenomegaly. In some cases, an elevated white blood count is discovered incidentally. Rarely, the patient will present with a clinical syndrome related to leukostasis with blurred vision, respiratory distress, or priapism. The white blood count in these cases is usually greater than 100,000/mcL (100×10^9/L) but less than 500,000/mcL (500×10^9/L). On examination, the spleen is enlarged (often markedly so), and sternal tenderness may be present as a sign of marrow overexpansion. In cases discovered during routine laboratory monitoring, these findings are often absent. Acceleration of the disease is often associated with fever (in the absence of infection), bone pain, and splenomegaly.

B. Laboratory Findings

CML is characterized by an elevated WBC count; the median white blood count at diagnosis is 150,000/mcL (150×10^9/L), although in some cases the WBC count is only modestly increased (Table 13–14). The peripheral blood is characteristic. The myeloid series is left shifted, with mature forms dominating and with cells usually present in proportion to their degree of maturation. Blasts are usually less than 5%. Basophilia and eosinophilia may be present. At presentation, the patient is usually not anemic. RBC morphology is normal, and nucleated RBCs are rarely seen. The platelet count may be normal or elevated (sometimes to strikingly high levels). A bone marrow biopsy is essential to ensure sufficient material for a complete karyotype and for morphologic evaluation to confirm the phase of disease. The bone marrow is hypercellular, with left-shifted myelopoiesis. Myeloblasts compose less than 5% of marrow cells. The hallmark of the disease is the *bcr/abl* gene that is detected by PCR testing of the peripheral blood and bone marrow.

With progression to the accelerated and blast phases, progressive anemia and thrombocytopenia occur, and the percentage of blasts in the blood and bone marrow increases. Blast-phase CML is diagnosed when blasts comprise more than 20% of bone marrow cells.

Differential Diagnosis

Early CML must be differentiated from the reactive leukocytosis associated with infection. In such cases, the white blood count is usually less than 50,000/mcL (50×10^9/L), splenomegaly is absent, and the *bcr/abl* gene is not present.

CML must be distinguished from other myeloproliferative disease (Table 13–14). The hematocrit should not be elevated, the RBC morphology is normal, and nucleated RBCs are rare or absent. Definitive diagnosis is made by finding the *bcr/abl* gene.

Treatment

Treatment is usually not emergent even with white blood counts over 200,000/mcL (200×10^9/L), since the majority of circulating cells are mature myeloid cells that are smaller and more deformable than primitive leukemic blasts. In the rare instances in which symptoms result from extreme hyperleukocytosis (priapism, respiratory distress, visual blurring, altered mental status), emergent leukapheresis is performed in conjunction with myelosuppressive therapy.

In chronic-phase CML, the goal of therapy is normalization of the hematologic abnormalities and suppression of the malignant *bcr/abl*-expressing clone. The treatment of choice consists of a tyrosine kinase inhibitor (eg, imatinib, nilotinib, dasatinib, bosutinib) targeting the aberrantly active abl kinase. It is expected that a hematologic complete remission, with normalization of blood counts and splenomegaly will occur within 3 months of treatment initiation. Second, a reduction of *bcr/abl* transcripts to less than 10% on the international scale should be achieved, ideally within 3 months but certainly within 6 months. Finally, a major molecular response (less than or equal to 0.1% transcripts) is desired within 12 months. Patients who achieve this level of molecular response have an excellent prognosis, with overall survival approaching 100% since disease progression is uncommon. On the other hand, patients have a worse prognosis if these targets are not achieved, molecular response is subsequently lost, or new pathogenic variants or cytogenetic abnormalities develop.

Imatinib mesylate was the first tyrosine kinase inhibitor to be approved and it results in nearly universal (98%) hematologic control of chronic-phase disease at a dose of 400 mg/day. The rate of a major molecular response with imatinib in chronic-phase disease is ~30% at 1 year. The second-generation tyrosine kinase inhibitors, nilotinib, dasatinib, and bosutinib are also used as front-line therapy and can significantly increase the rate of a major molecular response compared to imatinib and result in a lower rate of progression to advanced-stage disease. However, these agents are associated with additional toxicity and have not been shown to benefit overall survival. Since they can still salvage 90% of patients who do not respond to treatment with imatinib, they may be reserved for use in that situation.

Patients taking tyrosine kinase inhibitors should be monitored with a quantitative PCR assay. Those with a consistent increase in *bcr/abl* transcript or those with a suboptimal molecular response as defined above should undergo testing for a pathogenic variant of *abl* and then be switched to an alternative tyrosine kinase inhibitor. The *T315I* variant of *abl* is specifically resistant to therapy with imatinib, dasatinib, nilotinib, and bosutinib but appears to be sensitive to the third-generation agent ponatinib. However, ponatinib is associated with a high rate of vascular thrombotic complications. For patients with the *T315I* variant as well as patients who have not responded to multiple tyrosine kinase inhibitors, including ponatinib, the allosteric inhibitor asciminib can be tried. It has shown a 54% complete hematologic response rate and a 48% sustained major molecular response in heavily pretreated patients. Dose-limiting toxic effects include asymptomatic elevations in the lipase level and clinical pancreatitis. Lastly, omacetaxine—a non–tyrosine kinase inhibitor therapy approved for patients with CML who are resistant to at least two tyrosine kinase inhibitors—can produce major cytogenetic responses in 18% of patients. Patients in whom a good molecular response to any of these agents cannot be

achieved or in whom disease progresses despite therapy should be considered for allogeneic stem cell transplantation.

Patients with advanced-stage disease (accelerated phase or myeloid/lymphoid blast crisis) should be treated with a tyrosine kinase inhibitor alone or in combination with myelosuppressive chemotherapy. The doses of tyrosine kinase inhibitors in that setting are usually higher than those appropriate for chronic-phase disease. Since the duration of response to tyrosine kinase inhibitors in this setting is limited, patients who have accelerated or blast-phase disease should ultimately be considered for allogeneic stem cell transplantation.

Course & Prognosis

Patients with good molecular responses to tyrosine kinase inhibitor therapy have an excellent prognosis, with essentially 100% survival at last follow up. Studies suggest that tyrosine kinase inhibitor therapy may be safely discontinued after 2 years in patients who achieve a sustained major molecular response, with ~50% of patients remaining in molecular remission at least 1 year posttreatment. Of importance, more than 80% of recurrences occur within the first 6–8 months after stopping therapy, and loss of major molecular response is uncommon after 1 year. About 90–95% of patients who experience molecular recurrence regain their initial molecular level after restarting tyrosine kinase inhibitor therapy.

When to Refer

All patients with CML should be referred to a hematologist.

When to Admit

Hospitalization is rarely necessary and should be reserved for symptoms of leukostasis at diagnosis or for transformation to acute leukemia.

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MYELODYSPLASTIC SYNDROMES

ESSENTIALS OF DIAGNOSIS

- Cytopenias with a hypercellular bone marrow.
- Morphologic abnormalities in one or more hematopoietic cell lines.

General Considerations

The MDS are a group of acquired clonal disorders of the hematopoietic stem cell. They are characterized by the constellation of cytopenias, a usually hypercellular marrow, morphologic dysplasia, and genetic abnormalities. The disorders are usually idiopathic but may be caused by prior exposure to cytotoxic chemotherapy, radiation, or both. In addition to cytogenetics, sequencing can detect genetic pathogenic variants in 80–90% of MDS patients. Importantly, acquired clonal variants identical to those seen in MDS can occur in the hematopoietic cells of ~10% of apparently healthy older individuals, defining the disorder of **clonal hematopoiesis of indeterminate potential (CHIP).**

Myelodysplasia encompasses several heterogeneous syndromes. A key distinction is whether there is an increase in bone marrow blasts (greater than 5% of marrow elements). The category of MDS with excess blasts represents a more aggressive form of the disease, often leading to AML. Those without excess blasts are characterized by the degree of dysplasia, eg, MDS with single lineage dysplasia and MDS with multilineage dysplasia. The morphologic finding of **ringed sideroblasts** is used to define a subcategory of the lower-risk MDS syndromes. Patients with **isolated 5q loss,** which is characterized by the cytogenetic finding of loss of part of the long arm of chromosome 5, comprise an important subgroup of patients with a different natural history. Lastly, a proliferative syndrome including sustained peripheral blood monocytosis more than 1000/mcL (1.0×10^9/L) is termed **chronic myelomonocytic leukemia (CMML),** a disorder that shares features of myelodysplastic and myeloproliferative disorders. An International Prognostic Scoring System (IPSS) classifies patients by risk status based on the percentage of bone marrow blasts, cytogenetics, and severity of cytopenias. The IPSS is associated with the rate of progression to AML and with overall survival, which can range from a median of 6 years for the low-risk group to 5 months for the high-risk patients.

Clinical Findings

A. Symptoms and Signs

Patients are usually over age 60 years. Many patients are asymptomatic when the diagnosis is made because of the finding of abnormal blood counts. Fatigue, infection, or bleeding related to bone marrow failure are usually the presenting symptoms and signs. The course may be indolent, and the disease may present as a wasting illness with fever, weight loss, and general debility. On examination, splenomegaly may be present in combination with pallor, bleeding, and various signs of infection. MDS can also be accompanied by a variety of paraneoplastic syndromes prior to or following this diagnosis.

B. Laboratory Findings

Anemia may be marked with the MCV normal or increased, and transfusion support may be required. On the peripheral blood smear, macro-ovalocytes may be seen. The WBC count is usually normal or reduced, and neutropenia is common.

The neutrophils may exhibit morphologic abnormalities, including deficient numbers of granules or deficient segmentation of the nucleus, even a bilobed nucleus (the so-called Pelger-Huët abnormality). The myeloid series may be left shifted, and small numbers of promyelocytes or blasts may be seen. The platelet count is normal or reduced, and hypogranular platelets may be present.

The bone marrow is characteristically hypercellular but occasionally may be hypocellular. Erythroid hyperplasia is common, and signs of abnormal erythropoiesis include megaloblastic features, nuclear budding, or multinucleated erythroid precursors. The Prussian blue stain may demonstrate ringed sideroblasts. In the marrow, too, the myeloid series is often left shifted, with variable increases in blasts. Deficient or abnormal granules may be seen. A characteristic abnormality is the presence of dwarf megakaryocytes with a unilobed nucleus. Genetic abnormalities define MDS; there are frequent cytogenetic abnormalities involving chromosomes 5 and 7. Some patients with an indolent form have an isolated partial deletion of chromosome 5 (MDS with isolated del[5q]). Aside from cytogenetic abnormalities, the most commonly genes with pathogenic variants are *SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53,* and *EZH2.*

Differential Diagnosis

MDS should be distinguished from megaloblastic anemia, aplastic anemia, myelofibrosis, HIV-associated cytopenias, and acute or chronic drug effect. In subtle cases, cytogenetic evaluation of the bone marrow may help distinguish this clonal disorder from other causes of cytopenias. As the number of blasts increases in the bone marrow, myelodysplasia is arbitrarily separated from AML by the presence of less than 20% blasts.

Treatment

Myelodysplasia is a heterogeneous disease, and the appropriate treatment depends on a number of factors. For patients with anemia who have a low serum erythropoietin level (500 U/L or less), erythropoiesis-stimulating agents may raise the hematocrit and reduce the RBC transfusion requirement in 40%. Addition of intermittent granulocyte colony-stimulating factor (G-CSF) therapy may augment the erythroid response to epoetin. Unfortunately, the patients with the highest transfusion requirements and those with erythropoietin levels above 200 U/L are the least likely to respond. Patients who remain dependent on RBC transfusion and who can tolerate it should receive iron chelation in order to prevent serious iron overload; the dose of oral agent deferasirox is 20 mg/kg/day in divided dosing. Patients affected primarily with severe neutropenia may benefit from the use of myeloid growth factors such as filgrastim. Oral thrombopoietin analogs, such as romiplostim and eltrombopag, have shown effectiveness in raising the platelet count in myelodysplasia. Finally, occasional patients can benefit from immunosuppressive therapy including ATG. Predictors of response to ATG include age younger than 60 years, absence of 5q–, and presence of HLA DR15.

For patients who do not respond to these interventions, there are several therapeutic options available. Lenalidomide is the treatment of choice in patients with MDS with isolated del(5q) with significant responses in 70% of patients, and responses typically lasting longer than 2 years. In addition, nearly half of these patients enter a cytogenetic remission with clearing of the abnormal 5q– clone. The recommended initial dose is 10 mg/day orally. The most common side effects are neutropenia and thrombocytopenia, but venous thrombosis occurs and warrants prophylaxis with aspirin, 81 mg/day orally. A novel agent, luspatercept, has been developed to target signaling via the SMAD2–SMAD3 pathway, which is constitutively increased in the bone marrow cells of patients with MDS and ineffective erythropoiesis. In a randomized study, luspatercept induced transfusion independence in 38% of lower-risk MDS patients who had not responded to growth factor therapy compared to 13% in the placebo arm. The most common adverse events included fatigue, diarrhea, asthenia, nausea, and dizziness.

For patients with high-risk MDS, hypomethylating agents are the treatment of choice. Azacitidine can improve both symptoms and blood counts and prolong overall survival and time to conversion to acute leukemia. It is used at a dose of 75 mg/m^2 daily for 5–7 days every 28 days and up to six cycles of therapy may be required to achieve a response. Decitabine, a related hypomethylating agent, given at 20 mg/m^2 daily for 5 days every 28 days can produce similar hematologic responses but has not demonstrated a benefit in overall survival compared to supportive care alone. Unfortunately, the progress that has been made over the past decade in understanding the complex molecular mechanisms underlying MDS has not yet translated into new therapeutic options. The addition of the BCL2 inhibitor venetoclax to 5-azacytidine has recently been shown to be well tolerated and may lead to higher response rates.

Allogeneic stem cell transplantation is the only curative therapy for myelodysplasia, but its role is limited by the advanced age of many patients and the variably indolent course of the disease.

Course & Prognosis

Myelodysplasia is an ultimately fatal disease, and allogeneic transplantation is the only curative therapy, with cure rates of 30–60% depending primarily on the risk status of the disease. Patients most commonly die of infections or bleeding. Patients with MDS with isolated del(5q) have a favorable prognosis, with 5-year survival over 90%. Other patients with low-risk disease (with absence of both excess blasts and adverse cytogenetics) may also do well, with similar survival. Those with excess blasts or CMML have a higher (30–50%) risk of developing acute leukemia, and short survival (less than 2 years) without allogeneic transplantation.

When to Refer

All patients with myelodysplasia should be referred to a hematologist.

When to Admit

Hospitalization is needed only for specific complications, such as severe infection.

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ACUTE LEUKEMIA

ESSENTIALS OF DIAGNOSIS

- Short duration of symptoms, including fatigue, fever, and bleeding.
- Cytopenias or pancytopenia.
- Blasts in peripheral blood in 90% of patients.
- More than 20% blasts in the bone marrow.

General Considerations

Acute leukemia is a malignancy of the hematopoietic progenitor cell. Malignant immature cells proliferate in an uncontrolled fashion and replace normal bone marrow elements. Most cases arise with no clear cause. However, radiation and some toxins (benzene) are leukemogenic. In addition, a number of chemotherapeutic agents (especially cyclophosphamide, melphalan, other alkylating agents, and etoposide) may cause leukemia. The leukemias seen after toxin or chemotherapy exposure often develop from a myelodysplastic prodrome and are often associated with abnormalities in chromosomes 5 and 7. Those related to etoposide or anthracyclines may have abnormalities in chromosome 11q23 (MLL locus).

Most of the clinical findings in acute leukemia are due to replacement of normal bone marrow elements by the malignant cells. Less common manifestations result from organ infiltration (skin, GI tract, meninges). Acute leukemia is potentially curable with combination chemotherapy.

The myeloblastic subtype, AML, is primarily an adult disease with a median age at presentation of 60 years and an increasing incidence with advanced age. Acute promyelocytic leukemia (APL) is characterized by the chromosomal translocation t(15;17), which produces the fusion gene *PML-RAR*-alpha, leading to a block in differentiation that can be overcome with pharmacologic doses of retinoic acid. The lymphoblastic subtype of acute leukemia, ALL, comprises 80% of the acute leukemias of childhood. The peak incidence is between 3 and 7 years of age. It is also seen in adults, causing approximately 20% of adult acute leukemias.

Classification of the Leukemias

A. Acute Myeloid Leukemia (AML)

AML is primarily categorized based on recurrent structural chromosomal and molecular abnormalities. The cytogenetic abnormalities can be identified on traditional karyotyping or metaphase fluorescence in situ hybridization (FISH) and the molecular abnormalities are identified by either targeted or genome-wide sequencing of tumor DNA. Favorable cytogenetics such as t(8;21) producing a chimeric RUNX1/RUNX1T1 protein and inv(16)(p13;q22) are seen in 15% of cases and are termed the "core-binding factor" leukemias. These patients have a higher chance of achieving both short- and long-term disease control. Unfavorable cytogenetics confer a very poor prognosis. These consist of chromosomal translocations [t(6;9), t(3;3) or inv (3), t(v;11q23)], isolated monosomy 5 or 7, the presence of two or more other monosomies, or three or more separate cytogenetic abnormalities and account for 25% of the cases. The majority of cases of AML are of intermediate risk by traditional cytogenetics and have either a normal karyotype or chromosomal abnormalities that do not confer strong prognostic significance. However, there are several recurrent gene pathogenic variants with prognostic significance in this subgroup. On the one hand, internal tandem duplication in the gene *FLT3* occurs in ~30% of AML and is conditionally associated with a poor prognosis in the setting of wild type *NPM1*. Other pathogenic variants conferring a poor prognosis occur in *RUNX1*, *ASXL1*, and *TP53*. On the other hand, a relatively favorable group of patients has been identified that lacks *FLT3-ITD* pathogenic variants and includes variants of nucleophosmin 1 (*NPM1*) or carries *CEBPA* biallelic variants.

B. Acute Promyelocytic Leukemia (APL)

In considering the various types of AML, APL is discussed separately because of its unique biologic features and response to non-chemotherapy treatments. APL is characterized by the cytogenetic finding of t(15;17) and the fusion gene *PML-RAR*-alpha. It is a highly curable form of leukemia (over 90%) with integration of all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) in induction, consolidation, and maintenance regimens.

C. Acute Lymphoblastic Leukemia (ALL)

ALL is most usefully classified by immunologic phenotype as follows: common, early B lineage, and T cell. Hyperdiploidy (with more than 50 chromosomes), especially of chromosomes 4, 10, and 17, and translocation t(12;21) (TEL-AML1), is associated with a better prognosis. Unfavorable cytogenetics are hypodiploidy (less than 44 chromosomes), the Philadelphia chromosome t(9;22), the t(4;11) translocation (which has fusion genes involving the *MLL* gene at 11q23), and a complex karyotype with more than five chromosomal abnormalities.

D. Mixed Phenotype Acute Leukemias

These leukemias consist of blasts that lack differentiation along the lymphoid or myeloid lineage or blasts that express both myeloid and lymphoid lineage-specific antigens. This group is considered very high risk and has a poor prognosis. The limited available data suggest that an "acute lymphoblastic leukemia–like" regimen followed by allogeneic stem cell transplant may be advisable; addition of a tyrosine kinase inhibitor in patients with t(9;22) translocation is recommended.

Clinical Findings

A. Symptoms and Signs

Most patients have been ill only for days or weeks. Bleeding (usually due to thrombocytopenia) occurs in the skin and mucosal surfaces, with gingival bleeding, epistaxis, or menorrhagia. Less commonly, widespread bleeding is seen in patients with disseminated intravascular coagulation (DIC) (in APL and monocytic leukemia). Infection is due to neutropenia, with the risk of infection rising as the neutrophil count falls below 500/mcL (0.5×10^9/L). Common presentations include cellulitis, pneumonia, and perirectal infections; death within a few hours may occur if treatment with appropriate antibiotics is delayed. Fungal infections are also commonly seen.

Patients may also seek medical attention because of gum hypertrophy and bone and joint pain. The most dramatic presentation is hyperleukocytosis, in which a markedly elevated circulating blast count (total white blood count greater than 100,000/mcL [100×10^9/L]) leads to impaired circulation, presenting as headache, confusion, and dyspnea. Such patients require emergent chemotherapy with adjunctive leukapheresis since mortality approaches 40% in the first 48 hours.

On examination, patients appear pale and have purpura and petechiae; signs of infection may not be present. Stomatitis and gum hypertrophy may be seen in patients with monocytic leukemia, as may rectal fissures. There is variable enlargement of the liver, spleen, and lymph nodes. Bone tenderness may be present, particularly in the sternum, tibia, and femur.

B. Laboratory Findings

The hallmark of acute leukemia is the combination of pancytopenia with circulating blasts. However, blasts may be absent from the peripheral smear in as many as 10% of cases ("aleukemic leukemia"). The bone marrow is usually hypercellular and dominated by blasts (greater than 20%).

Hyperuricemia may be seen. If DIC is present, the fibrinogen level will be reduced, the prothrombin time prolonged, and fibrin degradation products or fibrin D-dimers present. Patients with ALL (especially T cell) may have a mediastinal mass visible on chest radiograph. Meningeal leukemia will have blasts present in the spinal fluid, seen in approximately 5% of cases at diagnosis; it is more common in monocytic types of AML and can be seen with ALL.

The **Auer rod,** an eosinophilic needle-like inclusion in the cytoplasm, is a characteristic of AML (though sometimes seen in APL, high-grade MDS, and myeloproliferative disorders). The phenotype of leukemia cells is usually demonstrated by flow cytometry or immunohistochemistry. AML cells usually express myeloid antigens such as CD13 or CD33 and myeloperoxidase. ALL cells of B lineage will express CD19, and most cases will express CD10, formerly known as the "common ALL antigen." ALL cells of T lineage will usually not express mature T-cell markers, such as CD3, CD4, or CD8, but will express some combination of CD2, CD5, and CD7 and will not express surface immunoglobulin. Almost all cells express terminal deoxynucleotidyl transferase (TdT).

Differential Diagnosis

AML must be distinguished from other myeloproliferative disorders, CML, and MDS. Acute leukemia may also resemble a left-shifted bone marrow recovering from a previous toxic insult. If the diagnosis is in doubt, a bone marrow study should be repeated in several days to see if maturation has taken place. ALL must be separated from other lymphoproliferative disease such as CLL, lymphomas, and hairy cell leukemia. It may also be confused with the atypical lymphocytosis of mononucleosis and pertussis.

Treatment

Acute leukemia is considered a curable disease, especially among younger patients without significant comorbidities. The first step in treatment is to obtain complete remission, defined as normal peripheral blood with resolution of cytopenias, normal bone marrow with no excess blasts, and normal clinical status. The type of initial chemotherapy depends on the subtype of leukemia.

1. AML—Most patients with AML who are treated with a curative intent receive a combination of an anthracycline (daunorubicin or idarubicin) plus cytarabine, either alone or in combination with other agents (eg, gemtuzumab ozogamicin). This therapy will produce complete remissions in 80–90% of patients under age 60 years and in 50–60% of older patients (see Table 39–2). Patients with secondary AML (evolved from prior myelodysplastic or myeloproliferative disorders) or treatment-associated AML should receive the drug Vyxeos (a liposomal formulation of daunorubicin and cytarabine). Patients with a pathogenic variant of *FLT3* benefit from the addition of the FLT3 kinase inhibitor midostaurin to their regimen. Post-remission therapy options include additional chemotherapy and allogeneic stem cell transplantation. Patients with a favorable genetic profile can be treated with chemotherapy alone or with autologous transplant with cure rates of 60–80%. For intermediate-risk patients with AML, cure rates are 35–40% with chemotherapy and 40–60% with allogeneic transplantation. Patients who do not enter remission (primary induction failure) or those with high-risk genetics have cure rates of less than 10% with chemotherapy alone and are referred for allogeneic stem cell transplantation.

Patients who are not treated with initial curative intent (those older than 75 years or with significant comorbidities) can derive benefit from newer targeted agents, including the bcl2 inhibitor venetoclax added to a hypomethylating

agent or low-dose cytarabine, enasidenib (targeting *IDH2* mutations), ivosidenib (targeting *IDH2* mutations), or glasdegib. Some of these patients can still benefit from a reduced-intensity allogeneic transplant if they achieve good disease control.

Once leukemia has recurred after initial chemotherapy, the prognosis is poor. For patients in second remission, allogeneic transplantation offers a 20–30% chance of cure. Targeted therapies described above are useful for selected patients and can offer long-term disease control.

2. ALL—Adults with ALL are treated with combination chemotherapy, including daunorubicin, vincristine, prednisone, and asparaginase. This treatment produces complete remissions in 90% of patients. Those patients with Philadelphia chromosome-positive ALL (or *bcr-abl*-positive ALL) should receive a tyrosine kinase inhibitor, such as dasatinib or ponatinib, added to their initial chemotherapy. Remission induction therapy for ALL is less myelosuppressive than treatment for AML and does not necessarily produce prolonged marrow aplasia. Patients should also receive CNS prophylaxis so that meningeal sequestration of leukemic cells does not develop.

After achieving complete remission, patients may be treated with either additional cycles of chemotherapy or high-dose chemotherapy and stem cell transplantation. Treatment decisions are made based on patient age and disease risk factors. Adults younger than 39 years have uniformly better outcomes when treated under pediatric protocols. For older patients, minimal residual disease testing early on can identify high-risk patients who will not be cured with chemotherapy alone and who will do better with allogeneic transplantation. For patients with relapsed disease, the bispecific antibody blinatumomab targeting CD19 and the antibody-drug conjugate inotuzumab ozogamicin targeting CD22 have shown remarkable activity and are considered superior to traditional chemotherapy options. Chimeric antigen receptor T cell therapy targeting CD19 is an additional option for patients with relapsed or refractory B-ALL but is currently used as a bridge to allogeneic transplantation.

Prognosis

Approximately 70–80% of adults with AML under age 60 years achieve complete remission and ~50% are cured using risk-adapted post-remission therapy. Older adults with AML achieve complete remission in up to 50% of instances. The cure rates for older patients with AML have been very low (approximately 10–20%) even if they achieve remission and are able to receive post-remission chemotherapy.

Patients younger than 39 years with ALL have excellent outcomes after undergoing chemotherapy followed by risk-adapted intensification and transplantation (cure rates of 60–80%). Patients with adverse cytogenetics, poor response to chemotherapy, or older age have a much lower chance of cure (cure rates of 20–40%).

When to Refer

All patients should be referred to a hematologist.

When to Admit

Most patients with acute leukemia will be admitted for treatment.

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CHRONIC LYMPHOCYTIC LEUKEMIA

ESSENTIALS OF DIAGNOSIS

- B-cell lymphocytosis with CD19 expression > 5000/mcL (> 5.0×10^9/L).
- Coexpression of CD19, CD5 on lymphocytes.

General Considerations

CLL is a clonal malignancy of B lymphocytes. The disease is usually indolent, with slowly progressive accumulation of long-lived small lymphocytes. These cells are immune-incompetent and respond poorly to antigenic stimulation.

CLL is manifested clinically by immunosuppression, bone marrow failure, and organ infiltration with lymphocytes. Immunodeficiency is also related to inadequate antibody production by the abnormal B cells. With advanced disease, CLL may cause damage by direct tissue infiltration.

CLL usually pursues an indolent course, but some subtypes behave more aggressively; a variant, prolymphocytic leukemia, is more aggressive. The morphology of the latter is different, characterized by larger and more immature cells. In 5–10% of cases, CLL may be complicated by autoimmune hemolytic anemia or autoimmune thrombocytopenia. In approximately 5% of cases an aggressive large-cell lymphoma (**Richter syndrome**) can develop.

Clinical Findings

A. Symptoms and Signs

CLL is a disease of older patients, with 90% of cases occurring after age 50 years and a median age at presentation of 70 years. Many patients will be incidentally discovered to have lymphocytosis. Others present with fatigue or lymphadenopathy. On examination, 80% of patients will have diffuse lymphadenopathy and 50% will have enlargement of the liver or spleen.

The long-standing Rai classification system remains prognostically useful: stage 0, lymphocytosis only; stage I, lymphocytosis plus lymphadenopathy; stage II, organomegaly (spleen, liver); stage III, anemia; stage IV, thrombocytopenia. These stages can be collapsed into low risk (stages 0–I), intermediate risk (stage II), and high risk (stages III–IV).

B. Laboratory Findings

The hallmark of CLL is isolated lymphocytosis. The WBC count is elevated and may be markedly abnormal (elevated to several hundred thousand). Usually 75–98% of the circulating cells are lymphocytes. Lymphocytes appear small and mature, with condensed nuclear chromatin, and are morphologically indistinguishable from normal lymphocytes, but smaller numbers of larger and activated lymphocytes may be seen. The hematocrit and platelet count are usually normal at presentation. The bone marrow is variably infiltrated with small lymphocytes. The immunophenotype of CLL demonstrates coexpression of the B lymphocyte lineage marker CD19 with the T lymphocyte marker CD5; this finding is commonly observed only in CLL and mantle cell lymphoma. CLL is distinguished from mantle cell lymphoma by the expression of CD23, CD200, and LEF-1, low expression of surface immunoglobulin and CD20, and the absence of a translocation or overexpression of cyclin D1. Patients whose CLL cells have pathogenic variants of the immunoglobulin gene (IgVH somatic mutation) have a more indolent form of disease; these cells typically express low levels of the surface antigen CD38 and do not express the zeta-associated protein (ZAP-70). Conversely, patients whose cells have nonvariant IgVH genes and high levels of ZAP-70 expression do less well and require treatment sooner. The assessment of genomic changes by FISH provides important prognostic information. The finding of deletion of chromosome 17p (TP53) confers the worst prognosis, while deletion of 11q (ATM) confers an inferior prognosis to the average genotype, and isolated deletion of 13q has a more favorable outcome. Hypogammaglobulinemia is present in 50% of patients and becomes more common with advanced disease. In some, a small amount of IgM paraprotein is present in the serum.

Differential Diagnosis

Few syndromes can be confused with CLL. Viral infections producing lymphocytosis should be obvious from the presence of fever and other clinical findings; however, fever may occur in CLL from concomitant bacterial infection. Pertussis may cause a particularly high total lymphocyte count. Other lymphoproliferative diseases such as Waldenström macroglobulinemia, hairy cell leukemia, or lymphoma (especially mantle cell lymphoma or small lymphocyte lymphoma) in the leukemic phase are distinguished on the basis of the morphology and immunophenotype of circulating lymphocytes and bone marrow. Monoclonal B-cell lymphocytosis is a disorder characterized by fewer than 5000/mcL (5.0×10^9/L) B cells and is considered a precursor to B-CLL.

Treatment

The treatment of CLL is evolving as several active targeted agents are now available. Most cases of early indolent CLL require no specific therapy, and the standard of care for early-stage disease has been observation. Indications for treatment include progressive fatigue, symptomatic lymphadenopathy, anemia, or thrombocytopenia. These patients have either symptomatic and progressive Rai stage II disease or stage III/IV disease. Initial treatment for patients with CLL consists of targeted biologic therapy in most cases. Options include single agent ibrutinib or acalabrutinib (inhibitors of Bruton tyrosine kinase that target B-cell receptor signaling) or venetoclax (a bcl2 inhibitor resulting in apoptosis) in combination with anti-CD20 antibody therapy. Choice between these agents is based on toxicity as well as preference. Ibrutinib is a well-tolerated, oral agent given at 420 mg daily; it can be associated with hypertension, atrial fibrillation, rash, and increased infections. Caution should be exercised when this agent is used in conjunction with CYP3A inhibitors or inducers. In addition, there is a potential for serious bleeding when it is used in patients taking warfarin. Acalabrutinib, a more specific BTK inhibitor, administered in a dose of 100 mg orally twice daily, is another option that is associated with a lower risk of adverse cardiovascular events. Venetoclax (slowly titrated up to 400 mg daily) is usually given for a shorter course of therapy and is associated with tumor lysis syndrome and neutropenia; some patients may require hospitalization for initial therapy. Venetoclax has to be combined with a monoclonal anti-CD20 antibody, usually obinutuzumab, which can result in infusion reactions. Traditional combination chemotherapy is used only in selected cases (see Table 39–3). For older patients, chlorambucil, 0.6–1 mg/kg orally every 4 weeks, in combination with obinutuzumab is another therapy option.

Patients who relapse while taking a BTK inhibitor should undergo testing to identify recurrent BTK pathogenic variants (eg, *C481S*) that may respond to the novel agent pirtobrutinib. Alternatively, they can be treated with a combination of venetoclax and the anti-CD20 antibody obinutuzumab. For patients who relapse following venetoclax-based therapy, a BTK inhibitor is often used. Other options for relapsed disease include idelalisib and duvelisib (inhibitors of PI3 kinase delta), which are associated with higher toxicity. The dosage for idelalisib is 150 mg orally twice a day, and the dosage for duvelisib is 25 mg orally twice a day. There are risks for colitis, liver injury, and fatal infectious complications in patients treated with PI3k inhibitors. Patients should be given antimicrobial prophylaxis and monitored closely while taking these agents.

Of note, BTK and PI3k inhibitors can be initially associated with marked lymphocytosis due to release of tumor cells from the lymph nodes into the peripheral blood. This results in a significant early reduction in lymphadenopathy but a potentially misleading, more delayed clearance of lymphocytes from peripheral blood and bone marrow.

Associated autoimmune hemolytic anemia or immune thrombocytopenia may require treatment with rituximab, prednisone, or splenectomy. Fludarabine should be avoided

in patients with autoimmune hemolytic anemia since it may exacerbate it. Rituximab should be used with anti-HBV agent prophylaxis in patients with past HBV infection. Patients with recurrent bacterial infections and hypogammaglobulinemia benefit from prophylactic infusions of gamma globulin (0.4 g/kg/month), but this treatment is cumbersome and expensive, justified only when these infections are severe. Patients undergoing therapy with a nucleoside analog (fludarabine, pentostatin) should receive anti-infective prophylaxis for *Pneumocystis jirovecii* pneumonia, herpes viruses, and invasive fungal infections until there is evidence of T-cell recovery.

Allogeneic transplantation offers potentially curative treatment for patients with CLL, but it should be used only in patients whose disease cannot be controlled by the available therapies. Nonmyeloablative allogeneic transplant can result in over 40% long-term disease control in CLL but with risk of moderate toxicity. Chimeric antigen receptor T-cell therapy is currently being evaluated for patients with refractory disease.

Prognosis

Targeted therapies have changed the prognosis of CLL. Patients with stage 0 or stage I disease have a median survival of 10–15 years, and these patients may be reassured that they can live a normal life. Patients with stage III or stage IV disease had a median survival of less than 2 years in the past, but with current therapies, 5-year survival is more than 70% and the long-term outlook appears to be substantially changed. For patients with high-risk and resistant forms of CLL, there is evidence that allogeneic transplantation can overcome risk factors and lead to long-term disease control.

When to Refer

All patients with CLL should be referred to a hematologist.

When to Admit

Hospitalization is rarely needed.

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HAIRY CELL LEUKEMIA

ESSENTIALS OF DIAGNOSIS

- Pancytopenia.
- Splenomegaly, often massive.
- Hairy cells present on blood smear and especially in bone marrow biopsy.

General Considerations

Hairy cell leukemia is a rare malignancy of hematopoietic stem cells differentiated as mature B lymphocytes with hairy cytoplasmic projections. The V600E pathogenic variant in the *BRAF* gene is recognized as the causal genetic event of hairy cell leukemia since it is detectable in almost all cases at diagnosis and is present at relapse.

Clinical Findings

A. Symptoms and Signs

The disease characteristically presents in middle-aged men. The median age at presentation is 55 years, and there is a striking 5:1 male predominance. Most patients present with gradual onset of fatigue, others complain of symptoms related to markedly enlarged spleen, and some come to attention because of infection.

Splenomegaly is almost invariably present and may be massive. The liver is enlarged in 50% of cases; lymphadenopathy is uncommon.

Hairy cell leukemia is usually an indolent disorder whose course is dominated by pancytopenia and recurrent infections, including mycobacterial infections.

B. Laboratory Findings

The hallmark of hairy cell leukemia is pancytopenia. Anemia is nearly universal, and 75% of patients have thrombocytopenia and neutropenia. The "hairy cells" are usually present in small numbers on the peripheral blood smear and have a characteristic appearance with numerous cytoplasmic projections. The bone marrow is usually inaspirable (dry tap), and the diagnosis is made by characteristic morphology on bone marrow biopsy. The hairy cells have a characteristic histochemical staining pattern with tartrate-resistant acid phosphatase (TRAP). On immunophenotyping, the cells coexpress the antigens CD11c, CD20, CD22, CD25, CD103, and CD123. Pathologic examination of the spleen shows marked infiltration of the red pulp with hairy cells. This is in contrast to the usual predilection of lymphomas to involve the white pulp of the spleen.

Differential Diagnosis

Hairy cell leukemia should be distinguished from other lymphoproliferative diseases that involve the bone marrow. It also may be confused with other causes of pancytopenia, including hypersplenism due to any cause, aplastic anemia, and paroxysmal nocturnal hemoglobinuria.

Treatment

Treatment is indicated for symptomatic disease, ie, splenic discomfort, recurrent infections, or significant cytopenias. The treatment of choice is a nucleoside analog, specifically pentostatin or cladribine for a single course, producing a complete remission in 70–95% of patients. Treatment is associated with infectious complications, and patients should be closely monitored. The median duration of response is over 8 years and patients who relapse a year or more after initial therapy can be treated again with one of

these agents. Rituximab can be used in the relapsed setting either as a single agent or in combination with a nucleoside analog. The BRAF inhibitor vemurafenib exhibits ~100% overall response rate in patients with refractory/relapsed hairy cell leukemia, with 35–40% complete remissions. The median relapse-free survival is ~19 months in patients who achieved complete remission and 6 months in those who obtained a partial response. Based on its superior safety profile compared to nucleoside analogs, vemurafenib is currently being evaluated as an initial therapy in combination with the anti-CD20 antibody obinutuzumab. Moxetumomab pasudotox is a recombinant CD22-targeting immunotoxin approved for patients with refractory disease. It has shown a durable complete response rate of 31% in the pivotal trial. However, it can be associated with capillary leak and hemolytic-uremic syndrome attributable to the diphtheria toxin moiety.

Course & Prognosis

More than 95% of patients with hairy cell leukemia live longer than 10 years.

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LYMPHOMAS

NON-HODGKIN LYMPHOMAS

ESSENTIALS OF DIAGNOSIS

- Often present with painless lymphadenopathy.
- Diagnosis is made by tissue biopsy.

General Considerations

The non-Hodgkin lymphomas are a heterogeneous group of cancers of lymphocytes usually presenting as enlarged lymph nodes. The disorders vary in clinical presentation and course from indolent to rapidly progressive.

Molecular biology has provided clues to the pathogenesis of these disorders, often a matter of balanced chromosomal translocations whereby an oncogene becomes juxtaposed next to either an immunoglobulin gene (B-cell lymphoma) or the T-cell receptor gene or related gene (T-cell lymphoma). The net result is oncogene overexpression and development of lymphoma. The best-studied example is Burkitt lymphoma, in which a characteristic cytogenetic abnormality of translocation between the long arms of chromosomes 8 and 14 has been identified. The protooncogene c-*myc* is translocated from its normal position on chromosome 8 to the immunoglobulin heavy chain locus on chromosome 14. Overexpression of c-*myc* is related to malignant transformation through excess B-cell proliferation. In follicular lymphoma, the t(14;18) translocation is characteristic and *bcl-2* is overexpressed, resulting in protection against apoptosis, the usual mechanism of B-cell death.

Classification of the lymphomas is a dynamic area still undergoing evolution. The 2017 grouping (Table 13–16) separates diseases based on both clinical and pathologic features. Eighty-five percent of non-Hodgkin lymphomas are B-cell and 15% are T-cell or NK-cell in origin. Even though non-Hodgkin lymphomas represent a diverse group of diseases, they are historically divided in two categories based on clinical behavior and pathology: the indolent (low-grade) and the aggressive (intermediate- or high-grade).

Table 13–16. World Health Organization classification of lymphomas (modified from 2017 version).

Precursor B-cell lymphoblastic lymphoma
Mature B-cell lymphomas
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
Hairy cell leukemia
Plasma cell myeloma
Diffuse large B-cell lymphoma
Primary diffuse large B-cell lymphoma of the CNS
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements
Mediastinal (thymic) large B-cell lymphoma
Follicular lymphoma
Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia)
Mantle cell lymphoma
Burkitt lymphoma
Marginal zone lymphoma
MALT type
Nodal type
Splenic type
Mature T- (and NK-) cell lymphomas
Anaplastic large-cell lymphoma
Angioimmunoblastic T-cell lymphoma
Peripheral T-cell lymphoma, NOS
Cutaneous T-cell lymphoma (mycosis fungoides, Sézary syndrome)
Extranodal NK-/T-cell lymphoma, nasal type
Adult T-cell leukemia/lymphoma
T-cell large granular lymphocytic leukemia
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classic Hodgkin lymphoma
Posttransplant lymphoproliferative disorders
Histiocytic and dendritic cell neoplasms

MALT, mucosa-associated lymphoid tissue; NOS, not otherwise specified.

Clinical Findings

A. Symptoms and Signs

Patients with non-Hodgkin lymphomas usually present with lymphadenopathy. Involved lymph nodes may be present peripherally or centrally (in the retroperitoneum, mesentery, and pelvis). The indolent lymphomas are usually disseminated at the time of diagnosis, and bone marrow involvement is frequent. Many patients with lymphoma have constitutional symptoms such as fever, drenching night sweats, and weight loss of greater than 10% of prior body weight (referred to as "B symptoms").

On examination, lymphadenopathy may be isolated or diffuse, and extranodal sites of disease (such as the skin, GI tract, liver, and bone marrow) may be found. Patients with Burkitt lymphoma are noted to have abdominal pain or abdominal fullness because of the predilection of the disease for the abdomen.

Once a pathologic diagnosis is established, staging is done using a whole-body PET/CT scan, a bone marrow biopsy, and, in patients with high-grade lymphoma or intermediate-grade lymphoma with high-risk features, a lumbar puncture.

B. Laboratory Findings

The peripheral blood is usually normal even with extensive bone marrow involvement by lymphoma. Circulating lymphoma cells in the blood are not commonly seen.

Bone marrow involvement is manifested as paratrabecular monoclonal lymphoid aggregates. In some high-grade lymphomas, the meninges are involved and malignant cells are found with cerebrospinal fluid cytology. The serum LD, a useful prognostic marker, is incorporated in risk stratification of treatment.

The diagnosis of lymphoma is made by tissue biopsy. Needle aspiration may yield evidence for non-Hodgkin lymphoma, but a lymph node biopsy (or biopsy of involved extranodal tissue) is required for accurate diagnosis and classification.

Treatment

A. Indolent Lymphomas

The most common lymphomas in this group are follicular lymphoma, marginal zone lymphomas, and small lymphocytic lymphoma (SLL). The treatment of **indolent lymphomas** depends on the stage of disease and the clinical status of the patient. A small number of patients have limited disease with only one or two contiguous abnormal lymph node groups and may be treated with localized irradiation with curative intent. However, most patients (85%) with indolent lymphoma have disseminated disease at the time of diagnosis and are not considered curable. Historically, treatment of these patients has not affected overall survival; therefore, treatment is offered only when symptoms develop or for high tumor bulk. Following each treatment response, patients will experience a relapse at traditionally shorter intervals. Some patients will have temporary spontaneous remissions (8%). There are an increasing number of reasonable treatment options for indolent lymphomas, but no consensus exists on the best strategy. Treatment with rituximab (375 mg/m^2 intravenously weekly for 4 weeks) is commonly used either alone or in combination with chemotherapy and may be the only agent to affect overall survival in these disorders. Patients should be screened for hepatitis B because rare cases of fatal fulminant hepatitis have been described with the use of anti-CD20 monoclonal therapies without anti-HBV agent prophylaxis. Rituximab is added to chemotherapy regimens including bendamustine; cyclophosphamide, vincristine, and prednisone (R-CVP); and cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (see Table 39–2). The immunomodulatory agent lenalidomide in combination with anti-CD20 therapy is an alternative option with similar outcomes to chemotherapy. The regimens mentioned above can also be used for patients with relapsed disease. Other treatment options include the PI3K delta inhibitors (idelalisib, umbralisib, and duvalisib) and the PI3K alpha inhibitor (copanlisib). Chimeric antigen receptor T-cell therapy targeting CD19 is available for patients with at least two relapses. Stem cell transplantation (either allogeneic or autologous) is also an option for these patients.

Patients with mucosa-associated lymphoid tissue (MALT) tumors of the stomach may be appropriately treated with combination antibiotics directed against *H pylori* and with acid blockade but require frequent endoscopic monitoring. Alternatively, MALT tumors confined to the stomach can also be cured with whole-stomach radiotherapy. MALT tumors of the spleen are usually associated with hepatitis C and may remit following hepatitis C eradication therapy.

B. Aggressive Lymphomas

Patients with **diffuse large B-cell lymphoma** are treated with curative intent. Most patients are treated with six cycles of immunochemotherapy such as R-CHOP (see Table 39–2). Involved nodal radiotherapy may be added for patients with bulky or extranodal disease. About 25% of patients with diffuse large B-cell lymphoma have been identified as "double-protein expressors" with overexpression of MYC and BCL2 proteins by immunohistochemistry. While the outcomes with R-CHOP are inferior, no definitive alternative treatment recommendations can be made at this time. **High-grade lymphoma** with chromosomal translocations affecting *MYC*, such as t(8;14), and translocations affecting *BCL2*, such as t(14;18), or *BCL6* (3q27), also called "double-hit lymphoma," has a very aggressive course. Patients with this disease may do better with dose-adjusted R-EPOCH as front-line therapy.

Patients with diffuse large B-cell lymphoma or high-grade lymphoma who relapse after initial chemotherapy can still be cured by autologous hematopoietic stem cell transplantation if their disease remains responsive to chemotherapy. An additional or alternative potentially curative option is chimeric antigen receptor T-cell therapy targeting CD19 therapy, which produces durable complete response rates of ~40%.

Mantle cell lymphoma is not effectively treated with standard immunochemotherapy regimens. Intensive initial immunochemotherapy including autologous hematopoietic stem cell transplantation has been shown to improve outcomes. The BTK inhibitors ibrutinib, acalabrutinib, and zanubrutinib are active in relapsed or refractory patients with mantle cell lymphoma. Chimeric antigen receptor T cell therapy targeting CD19 therapy with brexucabtagene autoleucel shows promising activity in patients whose disease progresses after treatment with BTK inhibitors. Reduced-intensity allogeneic stem cell transplantation offers curative potential for selected patients. For **primary CNS lymphoma,** repetitive cycles of high-dose intravenous methotrexate with rituximab early in the treatment course produce better results than whole-brain radiotherapy and with less cognitive impairment.

Patients with **highly aggressive lymphomas** (Burkitt or lymphoblastic) require urgent, intense, cyclic chemotherapy in the hospital similar to that given for ALL, and they also require intrathecal chemotherapy as CNS prophylaxis.

Patients with **peripheral T-cell lymphomas** usually have advanced stage nodal and extranodal disease and typically have inferior response rates to therapy compared to patients with aggressive B-cell lymphomas. Autologous stem cell transplantation is often incorporated in first-line therapy. The antibody-drug conjugate brentuximab vedotin has significant activity in patients with CD30-positive peripheral T-cell lymphomas, such as anaplastic large-cell lymphoma. The combination of brentuximab vedotin with cyclophosphamide, *adriamycin*, and prednisone is the initial treatment of choice for CD30-positive peripheral T-cell lymphomas.

Prognosis

The median survival of patients with indolent lymphomas is 10–15 years. These diseases ultimately become refractory to chemotherapy. This often occurs at the time of histologic progression of the disease to a more aggressive form of lymphoma.

The International Prognostic Index is widely used to categorize patients with aggressive lymphoma into risk groups. Factors that confer adverse prognosis are age over 60 years, elevated serum LD, stage III or stage IV disease, more than one extranodal site of disease, and poor performance status. Cure rates range from more than 80% for low-risk patients (zero risk factors) to less than 50% for high-risk patients (four or more risk factors).

For patients who relapse after initial chemotherapy, autologous hematopoietic stem cell transplantation and chimeric antigen receptor T-cell therapy offer a 40–50% chance of long-term lymphoma-free survival.

The treatment of older patients with lymphoma has been difficult because of poorer tolerance of aggressive chemotherapy. The use of reduced-intensity regimens (eg, R-miniCHOP) with myeloid growth factors and prophylactic antibiotics are preferred.

When to Refer

All patients with lymphoma should be referred to a hematologist or an oncologist.

When to Admit

Admission is necessary only for specific complications of lymphoma or its treatment and for the treatment of all high-grade lymphomas.

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Westin JR et al. Efficacy and safety of CD19-directed CAR-T cell therapies in patients with relapsed/refractory aggressive B-cell lymphomas: observations from the JULIET, ZUMA-1, and TRANSCEND trials. Am J Hematol. 2021;96:1295. [PMID: 34310745]

HODGKIN LYMPHOMA

ESSENTIALS OF DIAGNOSIS

- Often painless lymphadenopathy.
- Constitutional symptoms may or may not be present.
- Pathologic diagnosis by lymph node biopsy.

General Considerations

Hodgkin lymphoma is characterized by lymph node biopsy showing Reed-Sternberg cells in an appropriate reactive cellular background. The malignant cell is derived from B lymphocytes of germinal center origin.

Clinical Findings

There is a bimodal age distribution, with one peak in the 20s and a second over age 50 years. Most patients seek medical attention because of a painless mass, commonly in the neck. Others may seek medical attention because of constitutional symptoms such as fever, weight loss, or drenching night sweats, or because of generalized pruritus. An unusual symptom of Hodgkin lymphoma is pain in an involved lymph node following alcohol ingestion.

An important feature of Hodgkin lymphoma is its tendency to arise within single lymph node areas and spread in an orderly fashion to contiguous areas of lymph nodes. Late in the course of the disease, vascular invasion leads to widespread hematogenous dissemination.

Hodgkin lymphoma is divided into two subtypes: classic Hodgkin (nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted) and non-classic Hodgkin (nodular lymphocyte predominant). Hodgkin lymphoma should be distinguished pathologically from other malignant lymphomas and may occasionally be confused with reactive lymph nodes seen in infectious mononucleosis, cat-scratch disease, or drug reactions (eg, phenytoin).

Patients undergo a staging evaluation to determine the extent of disease, including serum chemistries, whole-body PET/CT scan, and bone marrow biopsy.

Treatment

Chemotherapy is the mainstay of treatment for Hodgkin lymphoma, and ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) remains the standard first-line regimen due to its manageable toxicity. The substitution of the antibody-drug conjugate brentuximab vedotin for bleomycin (AAVD) has demonstrated somewhat superior progression-free survival and is frequently used for patients with higher risk disease. The more intense regimen, escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), is associated with increased toxicity and is reserved for patients with activity on an interim PET/CT scan after starting ABVD. Low-risk patients are those with stage I or II disease without bulky lymphadenopathy or evidence of systemic inflammation. They traditionally receive a combination of short-course chemotherapy with involved nodal radiotherapy, but involved nodal radiotherapy can be eliminated for those with an early negative PET/CT scan without a significant change in outcomes (see Table 39–3). High-risk patients are those with stage III or IV disease or with stage II disease and a large mediastinal or other bulky mass or systemic inflammation. These patients are treated with a full course of chemotherapy for six cycles. Pulmonary toxicity can unfortunately occur following either chemotherapy (bleomycin) or radiation and should be treated aggressively in these patients, since it can lead to permanent fibrosis and death. A negative interim PET/CT scan after two cycles of chemotherapy can be used to identify patients with an excellent progression-free survival who can have bleomycin eliminated from their treatment. Conversely, an abnormal interim PET/CT scan is associated with a worse prognosis and should prompt early intensification of treatment to achieve a complete response (CR).

Classic Hodgkin lymphoma relapsing after initial treatment is treatable with high-dose chemotherapy and autologous hematopoietic stem cell transplantation. This offers a 35–50% chance of cure when disease is still chemotherapy responsive. Immune checkpoint inhibition by PD1 blockade with nivolumab or pembrolizumab has shown remarkable activity in patients with relapsed or refractory disease (overall response rate [ORR], 65%). These agents as well as brentuximab vedotin are increasingly incorporated in second-line regimens prior to or, for ineligible patients, in lieu of stem cell transplantation.

Prognosis

All patients should be treated with curative intent. Prognosis in advanced stage Hodgkin lymphoma is influenced by seven features: stage, age, gender, hemoglobin, albumin, WBC count, and lymphocyte count. The cure rate is 75% if zero to two risk features are present and 55% when three or more risk features are present. The prognosis of patients with stage IA or IIA disease is excellent, with 10-year survival rates in excess of 90%. Patients with advanced disease (stage III or IV) have 10-year survival rates of 50–60%. Inferior results are seen in patients who are older, those who have bulky disease, and those with lymphocyte depletion or mixed cellularity on histologic examination. Non-classic Hodgkin lymphoma (nodular lymphocyte predominant) is highly curable with radiotherapy alone for early-stage disease; however, for high-stage disease, it is characterized by long survival with repetitive relapses after chemotherapy or monoclonal anti-CD20 antibody therapy.

When to Refer

- All patients should be sent to an oncologist or hematologist.
- Secondary referral to a radiation oncologist might be appropriate.

When to Admit

Patients should be admitted for complications of the disease or its treatment.

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PLASMA CELL MYELOMA

ESSENTIALS OF DIAGNOSIS

- Bone pain, often in the spine, ribs, or proximal long bones.
- Monoclonal immunoglobulin (ie, paraprotein) in the serum or urine.
- Clonal plasma cells in the bone marrow or in a tissue biopsy, or both.
- Organ damage due to plasma cells (eg, bones, kidneys, hypercalcemia, anemia) or other defined criteria.

General Considerations

Plasma cell myeloma (previously called multiple myeloma) is a malignancy of hematopoietic stem cells

terminally differentiated as plasma cells. It is characterized by infiltration of the bone marrow, bone destruction, and paraprotein production. The diagnosis is established when monoclonal plasma cells (either kappa or lambda light chain restricted) are found in the bone marrow (any percentage) or in a tumor (plasmacytoma). This is associated with end-organ damage (such as bone disease [lytic lesions seen on bone radiographs, MRI, or PET/CT scan], anemia [hemoglobin less than 10 g/dL {100 g/L}], hypercalcemia [calcium greater than 11 mg/dL {2.75 mmol/L}], or kidney injury [creatinine greater than 2 mg/dL {176.8 mcmol/L} or creatinine clearance less than 40 mL/minute]) with or without paraprotein elaboration. Sixty percent or more clonal plasma cells in the bone marrow, or a serum free kappa to lambda ratio of greater than 100 or less than 0.01 (both criteria regardless of end-organ damage), are also diagnostic of plasma cell myeloma. Smoldering myeloma is defined as 10–59% clonal plasma cells in the bone marrow, a serum paraprotein level of 3 g/dL (30 g/L) or higher, or both, without plasma cell–related end-organ damage.

Malignant plasma cells can form tumors (plasmacytomas) that may cause spinal cord compression or other soft-tissue–related problems. Bone disease is common and due to excessive osteoclast activation mediated largely by the interaction of the receptor activator of NF-kappa-B (RANK) with its ligand (RANKL). In plasma cell myeloma, osteoprotegerin (a decoy receptor for RANKL) is underproduced, thus promoting the binding of RANK with RANKL with consequent excessive bone resorption.

The paraproteins (monoclonal immunoglobulins) secreted by the malignant plasma cells may cause additional problems. Very high paraprotein levels (either IgG or IgA) may cause hyperviscosity, although this is more common with the IgM paraprotein as in Waldenström macroglobulinemia. The light chain component of the immunoglobulin, when produced in excess, often leads to kidney injury (frequently aggravated by hypercalcemia or hyperuricemia, or both). Light chain components may be deposited in tissues as amyloid, resulting in kidney failure with albuminuria and a vast array of other systemic syndromes (restrictive cardiomyopathy, autonomic and peripheral neuropathy, enlarged tongue, etc).

Myeloma patients are prone to recurrent infections for a number of reasons, including neutropenia, the underproduction of normal immunoglobulins (so-called immunoparesis), and the immunosuppressive effects of chemotherapy. Myeloma patients are especially prone to infections with encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* and should receive vaccinations against them.

Clinical Findings

A. Symptoms and Signs

Myeloma is a disease of older adults (median age 65 years). The most common presenting complaints are those related to anemia, bone pain, kidney disease, and infection. Bone pain is most common in the back, hips, or ribs or may present as a pathologic fracture, especially of the femoral neck or vertebrae. Patients may also come to medical attention because of spinal cord compression from a plasmacytoma or the hyperviscosity syndrome (mucosal bleeding, vertigo, nausea, visual disturbances, alterations in mental status, hypoxia). Many patients are diagnosed because of laboratory findings of elevated total protein, hypercalcemia, proteinuria, elevated ESR, or abnormalities on serum protein electrophoresis obtained for symptoms or in routine screening studies. A few patients come to medical attention because of organ dysfunction due to amyloidosis.

Examination may reveal pallor, bone tenderness, or soft tissue masses. Patients may have neurologic signs related to neuropathy or spinal cord compression. Fever occurs mainly with infection. Acute oliguric or nonoliguric kidney injury may be present due to hypercalcemia, hyperuricemia, light chain cast injury, or primary amyloidosis.

B. Laboratory Findings

Anemia is nearly universal. RBC morphology is normal, but rouleaux formation is common and may be marked. The absence of rouleaux formation, however, excludes neither plasma cell myeloma nor the presence of a serum paraprotein. The neutrophil and platelet counts are usually normal at presentation. Only rarely will plasma cells be visible on peripheral blood smear (plasma cell leukemia if greater than 20%).

The hallmark of myeloma is the finding of a paraprotein on serum or urine protein electrophoresis (PEP) or immunofixation electrophoresis (IFE). The majority of patients will have a monoclonal spike visible in the gamma- or beta-globulin region of the PEP. The semi-quantification of the paraprotein on the PEP is referred to as the M-protein, and IFE will reveal this to be a monoclonal immunoglobulin. Approximately 15% of patients will have no demonstrable paraprotein in the serum on PEP because their myeloma cells produce only light chains and not intact immunoglobulin (but often seen on serum IFE), and the light chains pass rapidly through the glomerulus into the urine. Urine PEP and IFE usually demonstrate the light chain paraprotein in this setting. The free light chain assay will sometimes demonstrate excess monoclonal light chains in serum and urine, and in a small proportion of patients, will be the only means to identify and quantify the paraprotein being produced. Overall, the paraprotein is IgG (60%), IgA (20%), or light chain only (15%) in plasma cell myeloma, with the remainder being rare cases of IgD, IgM, or biclonal gammopathy. In sporadic cases, no paraprotein is present ("nonsecretory myeloma"); these patients have particularly aggressive disease.

The bone marrow will be infiltrated by variable numbers of monoclonal plasma cells. The plasma cells may be morphologically abnormal often demonstrating multi-nucleation and vacuolization. The plasma cells will display marked skewing of the normal kappa-to-lambda light chain ratio, which will indicate their clonality. Many benign inflammatory processes can result in bone marrow plasmacytosis, but with the absence of clonality and morphologic atypia.

C. Imaging

Bone radiographs are important in establishing the diagnosis of myeloma. Lytic lesions are most commonly seen in the axial skeleton: skull, spine, proximal long bones, and ribs.

At other times, only generalized osteoporosis is seen. The radionuclide bone scan is not useful in detecting bone lesions in myeloma since there is little osteoblastic component. In the evaluation of patients with known or suspected plasma cell myeloma, MRI and PET/CT scans are more sensitive to detect bone disease than plain radiographs and are preferred.

Differential Diagnosis

When a patient is discovered to have a paraprotein, the distinction between plasma cell myeloma or another lymphoproliferative malignancy with a paraprotein (CLL/SLL, Waldenström macroglobulinemia, non-Hodgkin lymphoma, primary amyloid, cryoglobulinemia) or monoclonal gammopathy of undetermined significance (MGUS) must be made. Plasma cell myeloma, smoldering plasma cell myeloma, and MGUS must be distinguished from reactive (benign) polyclonal hypergammaglobulinemia (which is commonly seen in cirrhosis or chronic inflammation).

Treatment

Patients with low-risk smoldering myeloma are observed. Those with high-risk smoldering disease may be treated with lenalidomide (an immunomodulatory agent) and dexamethasone since this therapy prolongs the time to symptomatic myeloma and may prolong survival compared to no treatment though at the expense of treatment-related side effects.

Most patients with plasma cell myeloma require treatment at diagnosis because of bone pain or other symptoms and complications related to the disease. The initial treatment generally involves therapy with an immunomodulatory agent, such as lenalidomide; a proteasome inhibitor, such as bortezomib or carfilzomib; the anti-CD38 monoclonal antibody, daratumumab; and moderate- or high-dose dexamethasone. An immunomodulatory agent is sometimes replaced with an alkylating agent, cyclophosphamide, in the setting of kidney injury. The major side effects of lenalidomide are neutropenia and thrombocytopenia, skin rash, venous thromboembolism, peripheral neuropathy, and possibly birth defects. Bortezomib and carfilzomib have the advantages of producing rapid responses and of being effective in poor-prognosis myeloma. The major side effect of bortezomib is neuropathy (both peripheral and autonomic), which is largely ameliorated when given subcutaneously rather than intravenously. Carfilzomib rarely causes neuropathy but sometimes causes acute pulmonary hypertension or cardiac systolic dysfunction that is usually reversible. For patients with plasma cell myeloma, including newly diagnosed, autologous stem cell transplant–ineligible patients as well as relapsed or refractory patients, daratumumab (1800 mg) plus hyaluronidase-fihj (30,000 units) is administered subcutaneously into the abdomen over 3–5 minutes.

An oral proteasome inhibitor, ixazomib, is available for relapsed disease. Pomalidomide, an immunomodulatory agent, is effective as salvage therapy after relapse. Other salvage agents include daratumumab, elotuzumab (an anti-SLAMF7 monoclonal antibody), selinexor (causes cell cycle arrest and apoptosis), and belantamab mafodotin (an anti-BCMA antibody conjugated to a cytotoxic agent).

After initial therapy, many patients under age 80 years are consolidated with autologous hematopoietic stem cell transplantation following high-dose melphalan (an alkylating chemotherapeutic agent). Autologous stem cell transplantation prolongs both duration of remission and overall survival. Lenalidomide or thalidomide prolong remission and survival when given as posttransplant maintenance therapy but at the expense of an elevated rate of second malignancies. Proteasome inhibitors prolong remissions in high-risk patients after autologous stem cell transplantation. For patients with multi-agent refractory disease, chimeric antigen receptor T-cell therapy targeting the early plasma cell antigen BCMA has shown remarkable activity with response rates exceeding 70% and median duration of response of over 11 months.

Localized radiotherapy may be useful for palliation of bone pain or for eradicating tumor at the site of pathologic fracture. Vertebral collapse with its attendant pain and mechanical disturbance can be treated with vertebroplasty or kyphoplasty. Hypercalcemia and hyperuricemia should be treated aggressively with immobilization and hydration. The bisphosphonates (pamidronate or zoledronic acid) or the RANKL-inhibitor (denosumab) given intravenously monthly reduces pathologic fractures in patients with bone disease. These medications are important adjuncts in this subset of patients. The bisphosphonates are also used to treat myeloma-related hypercalcemia. However, long-term bisphosphonates have been associated with a risk of osteonecrosis of the jaw and other bony areas, so their use is limited to 1–2 years after definitive initial therapy in most patients. Myeloma patients with oliguric or anuric kidney disease at diagnosis due to high free light chain levels should be treated aggressively with chemotherapy and considered for therapeutic plasma exchange (to reduce the paraprotein burden) because return of kidney function can sometimes occur.

Prognosis

The outlook for patients with myeloma has been steadily improving for the past decade. The median survival of patients is more than 7 years. Patients with low-stage disease who lack high-risk genomic changes respond very well to treatment and derive significant benefit from autologous hematopoietic stem cell transplantation with survival approaching a decade. The International Staging System for myeloma relies on two factors: beta-2-microglobulin and albumin. Stage 1 patients have both beta-2-microglobulin less than 3.5 mg/L and albumin greater than 3.5 g/dL (survival more than 5 years). Stage 3 is established when beta-2-microglobulin is greater than 5.5 mg/L (survival less than 2 years). Stage 2 is established with values in between stage 1 and 3. Other adverse prognostic findings are an elevated serum LD or bone marrow genetic abnormalities established by FISH involving the immunoglobulin heavy chain locus at chromosome 14q32, multiple copies of the 1q21-23 locus, or 17p chromosome abnormalities (causing the loss or mutation of *TP53*).

When to Refer

All patients with plasma cell myeloma should be referred to a hematologist or an oncologist.

When to Admit

Hospitalization is indicated for treatment of AKI, hypercalcemia, or suspicion of spinal cord compression, for certain chemotherapy regimens, or for autologous hematopoietic stem cell transplantation.

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van de Donk NWCJ et al. CAR T-cell therapy for multiple myeloma: state of the art and prospects. Lancet Haematol. 2021;8:e446. [PMID: 34048683]

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

ESSENTIALS OF DIAGNOSIS

- Monoclonal immunoglobulin (ie, paraprotein) in the serum (< 3 g/dL [< 30 g/L]) or urine or both.
- Clonal plasma cells in the bone marrow < 10% (diagnostic).
- No symptoms and no organ damage from the paraprotein.

General Considerations

MGUS is present in 1% of all adults (3% of those over age 50 years and more than 5% of those over age 70 years). Among all patients with paraproteins, MGUS is far more common than plasma cell myeloma. MGUS is defined as bone marrow clonal plasma cells less than 10% in the setting of a paraprotein in the serum or urine or both (serum M-protein less than 3 g/dL [30 g/L]) and the absence of plasma cell–related end-organ damage. If an excess of serum free light chains (kappa or lambda) is established, the kappa to lambda ratio is 100 or less or 0.01 or greater (otherwise, this is diagnostic of plasma cell myeloma). In approximately one-quarter of cases, MGUS progresses to overt malignant disease in a median of one decade. The transformation of MGUS to plasma cell myeloma is approximately 1% per year. Two adverse risk factors for progression of MGUS to a plasma cell or lymphoid malignancy are an abnormal serum kappa to lambda free light chain ratio and a serum monoclonal protein (M-protein) level 1.5 g/dL or greater. Patients with MGUS have shortened survival (median 8.1 years vs 12.4 years for age- and sex-matched controls). In addition, 12% of patients with MGUS will convert to primary amyloidosis in a median of 9 years. Plasma cell myeloma, smoldering plasma cell myeloma, and MGUS must be distinguished from reactive (benign) polyclonal hypergammaglobulinemia (common in cirrhosis or chronic inflammation).

Laboratory Findings

To establish the diagnosis, serum and urine should be sent for PEP and IFE to search for a monoclonal protein; serum should be sent for free light chain analysis and quantitative immunoglobulins. Additional tests include a hemoglobin and serum albumin, calcium, and creatinine. If these additional tests are normal (or if abnormal but otherwise explained), then a bone marrow biopsy is usually deferred provided the serum M-protein is less than 3 g/dL (less than 30 g/L). In asymptomatic individuals, a skeletal survey (radiographs) is performed, but if there are some bone complaints or a question regarding bone disease, MRI or PET/CT imaging is preferred. MGUS is diagnosed if patients do not meet the criteria for smoldering plasma cell myeloma or plasma cell myeloma.

Treatment

Patients with MGUS are observed without treatment.

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WALDENSTRÖM MACROGLOBULINEMIA

ESSENTIALS OF DIAGNOSIS

- Monoclonal IgM paraprotein.
- Infiltration of bone marrow by plasmacytic lymphocytes.
- Absence of lytic bone disease.
- *L265P* pathogenic variant in the gene *MYD88*.

General Considerations

Waldenström macroglobulinemia is a syndrome of IgM hypergammaglobulinemia that occurs in the setting of a low-grade non-Hodgkin lymphoma characterized by B cells that are morphologically a hybrid of lymphocytes and plasma cells. These cells characteristically secrete the IgM

paraprotein, and many clinical manifestations of the disease are related to this macroglobulin.

Clinical Findings

A. Symptoms and Signs

This disease characteristically develops insidiously in patients in their 60s or 70s. Patients usually present with fatigue related to anemia. Hyperviscosity of serum may be manifested in a number of ways. Mucosal and GI bleeding is related to engorged blood vessels and platelet dysfunction. Other complaints include nausea, vertigo, and visual disturbances. Alterations in consciousness vary from mild lethargy to stupor and coma. The IgM paraprotein may also cause symptoms of cold agglutinin disease (hemolysis) or chronic demyelinating peripheral neuropathy.

On examination, there may be hepatosplenomegaly or lymphadenopathy. The retinal veins are engorged. Purpura may be present. There should be no bone tenderness.

B. Laboratory Findings

Anemia is nearly universal, and rouleaux formation is common, although the RBCs are agglutinated when the blood smear is prepared at room temperature. The anemia is related in part to expansion of the plasma volume by 50–100% due to the presence of the paraprotein. Other blood counts are usually normal. The abnormal plasmacytic lymphocytes may appear in small numbers on the peripheral blood smear. The bone marrow is characteristically infiltrated by the plasmacytic lymphocytes. The *L265P* pathogenic variant in *MYD88* is detectable in more than 90% of patients.

The hallmark of macroglobulinemia is the presence of a monoclonal IgM spike seen on serum PEP in the beta-globulin region. The serum viscosity is usually increased above the normal of 1.4–1.8 times that of water. Symptoms of hyperviscosity usually develop when the serum viscosity is over four times that of water, and marked symptoms usually arise when the viscosity is over six times that of water. Because paraproteins vary in their physicochemical properties, there is no strict correlation between the concentration of paraprotein and serum viscosity.

The IgM paraprotein may cause a positive antiglobulin (Coombs) test for complement and have cold agglutinin or cryoglobulin properties. If macroglobulinemia is suspected but the serum PEP shows only hypogammaglobulinemia, the test should be repeated while taking special measures to maintain the blood at 37°C, since the paraprotein may precipitate out at room temperature. Bone radiographs are normal, and there is no evidence of kidney injury.

Differential Diagnosis

Waldenström macroglobulinemia is differentiated from MGUS by the finding of bone marrow infiltration with monoclonal malignant cells. It is distinguished from CLL by bone marrow morphology, the absence of CD5 expression, and the absence of lymphocytosis, and it is distinguished from plasma cell myeloma by bone marrow morphology, the finding of the characteristic IgM paraprotein, and the absence of lytic bone disease.

Treatment

Patients with marked hyperviscosity syndrome (stupor, coma, pulmonary edema) should be treated on an emergency basis with plasmapheresis. On a chronic basis, some patients can be managed with periodic plasmapheresis alone. As with other indolent malignant lymphoid diseases, rituximab (375 mg/m^2 intravenously weekly for 4–8 weeks) has significant activity. However, a word of caution: the IgM often rises first after rituximab therapy before it falls and for patients with hyperviscosity, an additional cytotoxic agent needs to be initiated at the same time. Combination therapy is recommended for advanced disease (see Table 39–3) with addition of bendamustine showing excellent response rates. The oral BTK inhibitors ibrutinib (420 mg daily) and zanubrutinib (160 mg twice daily) have shown significant activity with a 90% response rate and a 73% major response rate that can result in durable remissions. Proteasome inhibitors (bortezomib, carfilzomib) and lenalidomide have also been shown to have activity in this disease. Autologous hematopoietic stem cell transplantation is reserved for relapsed or refractory patients.

Prognosis

Waldenström macroglobulinemia is an indolent disease with a median survival rate of 5 years, and 10% of patients are alive at 15 years.

When to Refer

All patients should be referred to a hematologist or an oncologist.

When to Admit

Patients should be admitted for treatment of hyperviscosity syndrome.

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AMYLOIDOSIS

ESSENTIALS OF DIAGNOSIS

- Congo red positive amyloid protein on tissue biopsy.
- Primary amyloid protein is kappa or lambda immunoglobulin light chain.
- Serum or urine (or both) light chain paraprotein.

General Considerations

Amyloidosis is a rare condition whereby a protein abnormally deposits in tissue resulting in organ dysfunction.

The propensity of a protein to be amyloidogenic is a consequence of disturbed translational or posttranslational protein folding and lack of consequential water solubility. The input of amyloid protein into tissues far exceeds its output, so amyloid build up inexorably proceeds to organ dysfunction and ultimately organ failure and premature death.

Amyloidosis is classified according to the type of amyloid protein deposited. The six main categories are **primary** (immunoglobulin light chain [AL]), **secondary** (serum protein A, produced in inflammatory conditions [AA]), **hereditary** (mutated transthyretin [TTR]; many others), **senile** (wild-type TTR; atrial natriuretic peptide; others), **dialysis-related** (beta-2-microglobulin, not filtered out by dialysis membranes [Abeta-2M]), and **LECT2** (associated with Latinx ethnicity). Amyloidosis is further classified as **localized** (amyloid deposits only in a single tissue type or organ) or, most common, **systemic** (widespread amyloid deposition).

Clinical Findings

A. Symptoms and Signs

Patients with **localized amyloidosis** have symptoms and signs related to the affected single organ, such as hoarseness (vocal cords) or proptosis and visual disturbance (orbits). Patients with **systemic amyloidosis** have symptoms and signs of unexplained medical syndromes, including heart failure (infiltrative/restrictive cardiomyopathy), nephrotic syndrome, malabsorption and weight loss, hepatic dysfunction, autonomic insufficiency, carpal tunnel syndrome (often bilateral), and sensorimotor peripheral neuropathy. Other symptoms and signs include an enlarged tongue; waxy, rough plaques on skin; contusions (including the periorbital areas); cough or dyspnea; and disturbed deglutition. These symptoms and signs arise insidiously, and the diagnosis of amyloidosis is generally made late in the disease process.

B. Laboratory Findings

The diagnosis of amyloid protein requires a tissue biopsy that demonstrates deposition of a pink interstitial substance in the tissue with the hematoxylin and eosin stain. This protein stains red with Congo red and becomes an apple-green color when the light is polarized. Amyloid is a triple-stranded fibril composed of the amyloid protein, amyloid protein P, and glycosaminoglycan. The amyloid fibrils form beta-pleated sheets as demonstrated by electron microscopy. In primary amyloidosis, the amyloid protein is either the kappa or lambda immunoglobulin light chain.

When systemic amyloidosis is suspected, a blind aspiration of the abdominal fat pad will reveal amyloid two-thirds of the time. If the fat pad aspiration is unrevealing, then the affected organ needs biopsy. In 90% of patients with primary amyloidosis, analysis of the serum and urine will reveal a kappa or lambda light chain paraprotein by PEP, IFE, or free light chain assay; in the remainder, mass spectroscopy demonstrates light chain in the tissue biopsy. Lambda amyloid is more common than kappa amyloid, a relative proportion opposite from normal B-cell stoichiometry. Most patients with primary amyloidosis have a small excess of kappa- or lambda-restricted plasma cells in the bone marrow (but less than 10%). The bone marrow may or may not demonstrate interstitial amyloid deposition or amyloid in the blood vessels.

Patients with primary cardiac amyloidosis have an infiltrative cardiomyopathy with thick ventricular walls on echocardiogram that sometimes shows a specific speckling pattern. Paradoxically, QRS voltages are low on ECG. Cardiac MRI has a distinctive delayed enhancement of gadolinium that is virtually diagnostic. With renal amyloid, albuminuria is present, which can be in the nephrotic range. Late in renal involvement, kidney function decreases (see Chapter 22, Renal Amyloidosis).

Differential Diagnosis

Amyloidosis must be distinguished from MGUS and plasma cell myeloma or other malignant lymphoproliferative disorders with an associated paraprotein. Of note, 12% of patients with MGUS will convert to primary amyloidosis in a median of 9 years. One-fifth of patients who have primary amyloidosis will meet the diagnostic criteria for plasma cell myeloma; conversely, 5% of patients with plasma cell myeloma will have amyloid deposition of their paraprotein at diagnosis.

Treatment

The treatment approach to primary amyloidosis closely resembles that of plasma cell myeloma. Prospective, randomized trials of plasma cell myeloma chemotherapy versus colchicine have demonstrated a survival benefit to chemotherapy. The goal is reduction of light chain production and thus tissue deposition as a means to arrest progressive end-organ dysfunction. Active agents in primary amyloidosis include melphalan, cyclophosphamide, dexamethasone, lenalidomide, bortezomib and daratumumab (see Table 39–3). As in plasma cell myeloma, autologous hematopoietic stem cell transplantation after high-dose melphalan is used in patients with reasonable organ function and a good performance status. The treatment-related mortality, however, is higher in patients with primary amyloidosis than in plasma cell myeloma (6% vs 1%). Some patients will demonstrate end-organ improvement after therapy. Agents are being developed that facilitate amyloid dissolution or correct protein folding abnormalities in the amyloid protein. Treatment of AA amyloid is treatment of the underlying cause of inflammation. Treatment of familial TTR is liver transplantation and of acquired or inherited TTR is tafamidis or inotersen.

Prognosis

Untreated primary amyloidosis is associated with progressive end-organ failure and premature death. There is no known cure for primary amyloidosis. Although virtually every tissue examined at autopsy will contain amyloid, patients with primary amyloidosis usually have one or two primary failing organs that clinically drive the presentation

and prognosis. The cardiac biomarkers BNP, N-terminal pro-BNP, and troponins T and I are prognostic in this disease regardless of overt clinical cardiac involvement. Historically, patients with predominantly cardiac or autonomic nerve presentations had survivals of 3–9 months, those with carpal tunnel syndrome or nephrosis had survivals of 1.5–3 years, and those with peripheral neuropathy had survivals of 5 years. These survivals are roughly doubled with plasma cell myeloma-like treatment. In those patients able to undergo autologous hematopoietic stem cell transplantation, the median survival is about 5 years (and approaches 10 years for those achieving a complete hematologic remission).

When to Refer

- All patients who have primary amyloidosis or in whom it is suspected should be referred to a hematologist or oncologist.
- Patients with hereditary amyloidosis should be referred to a hepatologist for consideration of liver transplantation.

When to Admit

- Patients with systemic amyloidosis require hospitalization to treat exacerbations of end-organ failure, including heart, liver, or kidney.
- Patients with primary amyloidosis require hospitalization to undergo autologous hematopoietic stem cell transplantation.

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BLOOD TRANSFUSIONS

Most blood products are leukoreduced in-line during acquisition and are thus prospectively leukocyte-poor. Leukoreduced blood products reduce the incidence of leukoagglutination reactions, platelet alloimmunization, transfusion-related acute lung injury, and CMV exposure.

RBC TRANSFUSIONS

RBC transfusions are given to raise the hemoglobin levels in patients with clinically significant anemia or to replace losses after acute bleeding episodes.

Preparations of RBCs for Transfusion

Several types of preparations containing RBCs are available (whole blood, packed RBCs, frozen RBCs, or autologous non-frozen RBCs).

A. Fresh Whole Blood

The advantage of whole blood for transfusion is the simultaneous presence of RBCs, plasma, and fresh platelets. Fresh whole blood is not absolutely necessary, since all the above components are available separately. The major indications for use of whole blood are cardiac surgery with hemorrhage or massive hemorrhage when more than 10 units of blood is required in a 24-hour period.

B. Packed RBCs

Packed RBCs are the component most commonly used to raise the hemoglobin. Each unit has a volume of about 300 mL, of which approximately 200 mL consists of RBCs. One unit of packed RBCs will usually raise the hemoglobin by approximately 1 g/dL. Current guidelines recommend a transfusion "trigger" hemoglobin threshold of 7–8 g/dL (70–80 g/L) for hospitalized patients, including those who are critically ill, those undergoing cardiothoracic surgery or repair of a hip fracture, those with upper GI bleeding, and those with hematologic malignancy undergoing chemotherapy or hematopoietic cell transplant.

C. Autologous Packed RBCs

Patients scheduled for elective surgery may donate blood for autologous transfusion. These units may be stored for up to 35 days before freezing is necessary.

Compatibility Testing

Before transfusion, the recipient's and the donor's blood are typed and cross-matched to avoid hemolytic transfusion reactions. Although many antigen systems are present on RBCs, only the ABO and Rh systems are specifically tested prior to all transfusions. The A and B antigens are the most important because everyone who lacks one or both RBC antigens has IgM isoantibodies (called isoagglutinins) in his or her plasma against the missing antigen(s). The isoagglutinins activate complement and can cause rapid intravascular lysis of the incompatible RBCs. In emergencies, type O/Rh-negative blood can be given to any recipient, but usually packed RBCs are given to minimize transfusion of donor plasma containing anti-A and anti-B antibodies with the use of whole blood.

The other important antigen routinely tested for is the D antigen of the Rh system. Approximately 15% of the population lacks this antigen. In patients lacking the antigen, anti-D antibodies are not naturally present, but the D antigen is highly immunogenic. A recipient whose RBCs lack D and who receives D-positive blood often develop anti-D antibodies that can cause severe lysis of subsequent transfusions of D-positive RBCs or abort a D-positive fetus.

Blood typing includes a cross-match assay of recipient serum for alloantibodies directed against donor RBCs by mixing recipient serum with panels of RBCs representing commonly occurring minor RBC antigens. The screening is particularly important if the recipient has had previous transfusions or pregnancy.

Hemolytic Transfusion Reactions

The most severe hemolytic transfusion reactions are acute (temporally related to the transfusion), involving incompatible mismatches in the ABO system that are isoagglutinin-mediated. Most of these cases are due to clerical errors and mislabeled specimens. With current compatibility testing and double-check clerical systems, the risk of an acute hemolytic reaction is 1 in 76,000 transfused units of RBCs. Death from acute hemolytic reaction occurs in 1 in 1.8 million transfused units. When hemolysis occurs, it is rapid and intravascular, releasing free hemoglobin into the plasma. The severity of these reactions depends on the dose of RBCs given. The most severe reactions are those seen in surgical patients under anesthesia.

Delayed hemolytic transfusion reactions are caused by minor RBC antigen discrepancies and are typically less severe. The hemolysis usually takes place at a slower rate and is mediated by IgG alloantibodies causing extravascular RBC destruction. These transfusion reactions may be delayed for 5–10 days after transfusion. In such cases, the recipient has received RBCs containing an immunogenic antigen, and in the time since transfusion, a new alloantibody has formed. The most common antigens involved in such reactions are Duffy, Kidd, Kell, and C and E loci of the Rh system. The current risk of a delayed hemolytic transfusion reaction is 1 in 6000 transfused units of RBCs.

A. Symptoms and Signs

Major acute hemolytic transfusion reactions cause fever and chills, with backache and headache. In severe cases, there may be apprehension, dyspnea, hypotension, and cardiovascular collapse. Patients under general anesthesia will not manifest such symptoms, and the first indication may be tachycardia, generalized bleeding, or oliguria. *The transfusion must be stopped immediately.* In severe cases, acute DIC, AKI from tubular necrosis, or both can occur. Death occurs in 4% of acute hemolytic reactions due to ABO incompatibility. Delayed hemolytic transfusion reactions are usually without any or only mild symptoms or signs.

B. Laboratory Findings

When an acute hemolytic transfusion episode is suspected, the identification of the recipient and of the transfusion product bag label should be rechecked. The transfusion product bag with its pilot tube must be returned to the blood bank, and a fresh sample of the recipient's blood must accompany the bag for retyping and re–cross-matching of donor and recipient blood samples. The hemoglobin will fail to rise by the expected amount after a transfusion. Coagulation studies may reveal evidence of AKI or acute DIC. The plasma-free hemoglobin in the recipient will be elevated resulting in hemoglobinuria.

In cases of delayed hemolytic reactions, there will be an unexpected drop in hemoglobin and an increase in the total and indirect bilirubins. The new offending alloantibody is easily detected in the patient's serum.

C. Treatment

If an acute hemolytic transfusion reaction is suspected, the transfusion should be stopped at once. The patient should be vigorously hydrated to prevent ATN. Forced diuresis with mannitol may help prevent or minimize AKI.

Leukoagglutinin Reactions

Most transfusion reactions are not hemolytic but represent reactions to antigens present on transfused passenger leukocytes in patients who have been sensitized to leukocyte antigens through previous transfusions or pregnancy. Transfusion products relatively rich in leukocyte-rich plasma, especially platelets, are most likely to cause this. Moderate to severe leukoagglutinin reactions occur in 1% of RBC transfusions and 2% of platelet transfusions. The risk of a leukoagglutination reaction is minimal if the transfused blood product is leukoreduced in-line upon collection. Most commonly, fever and chills develop in patients within 12 hours after transfusion. In severe cases, cough and dyspnea may occur and the chest radiograph may show transient pulmonary infiltrates. Because no hemolysis is involved, the hemoglobin rises by the expected amount despite the reaction.

Leukoagglutinin reactions may respond to acetaminophen (500–650 mg orally) and diphenhydramine (25 mg orally or intravenously); corticosteroids, such as hydrocortisone (1 mg/kg intravenously), are also of value. Overall, leukoagglutination reactions are diminishing through the routine use of in-line leukotrapping during blood donation (ie, leukoreduced blood). Patients experiencing severe leukoagglutination episodes despite receiving leukoreduced blood transfusions should receive leukopoor or washed blood products.

Hypersensitivity Reactions

Urticaria or bronchospasm may develop during or soon after a transfusion. These reactions are almost always due to exposure to allogeneic plasma proteins rather than to leukocytes. The risk is low enough that the routine use of antihistamine premedications has been eliminated before packed RBC transfusions. However, a hypersensitivity reaction, including anaphylactic shock, may develop in patients who are IgA deficient because of antibodies to IgA in the patient's plasma directed against the IgA in the transfused blood product. Patients with such reactions may require transfusion of washed or even frozen RBCs to avoid future severe reactions.

Contaminated Blood

Blood products can be contaminated with bacteria. Platelets are especially prone to bacterial contamination because they cannot be refrigerated. Bacterial contamination occurs in 1 of every 30,000 RBC donations and 1 of every 5000 platelet donations. Receipt of a blood product contaminated with gram-positive bacteria will cause fever and bacteremia, but rarely causes a sepsis syndrome. Receipt of a blood product contaminated with gram-negative bacteria often causes septic shock, acute DIC, and AKI due to the

transfused endotoxin and is usually fatal. Strategies to reduce bacterial contamination include enhanced venipuncture site skin cleansing, diverting of the first few milliliters of donated blood, use of single-donor blood products (as opposed to pooled-donor products), and point-of-care rapid bacterial screening in order to discard questionable units. Blood products infused with psoralen and then exposed to UVA light will have no living organisms in them but add cost to acquisition of the blood product. The current risk of a septic transfusion reaction from a culture-negative unit of single-donor platelets (not psoralen treated) is 1 in 60,000. In any patient who may have received contaminated blood, the recipient and the donor blood bag should both be cultured, and antibiotics should be given immediately to the recipient.

Infectious Diseases Transmitted Through Transfusion

Despite the use of only volunteer blood donors and the routine screening of blood, transfusion-associated viral diseases remain a problem. All blood products (RBCs, platelets, plasma, cryoprecipitate) can transmit viral diseases. All blood donors are screened with questionnaires designed to detect (and therefore reject) donors at high risk for transmitting infectious diseases. For example, the American Red Cross does not accept blood donation from persons with SARS-CoV-2 virus or from contacts of persons who have or are suspected to have the causal SARS-CoV-2 virus. All blood is screened for hepatitis B surface antigen, antibody to hepatitis B core antigen, antibody to syphilis, antibodies to HIV-1 and HIV-2 and NAT (nucleic acid amplification) for HIV, antibody to hepatitis C virus (HCV) and NAT for hepatitis C, antibody to human T-cell lymphotropic/leukemia virus (HTLV), and NAT for West Nile virus. Zika virus contamination is screened for by donor questionnaire, but the routine use of an FDA-approved detection test has not been uniformly adopted to screen donated blood. It is recommended that blood donors get screened once for antibodies against *Trypanosoma cruzi*, the infectious agent that causes Chagas disease (and if negative, no further screening for additional blood donations).

With improved screening, the risk of posttransfusion hepatitis has steadily decreased after the receipt of screened "negative" blood products. The risk of acquiring hepatitis B is about 1 in 200,000 transfused units in the United States. The risk of hepatitis C acquisition is 1 in 1.5 to 2 million transfused units in the United States. The risk of HIV acquisition is 1 in 2 million transfused units. Unscreened but leukoreduced blood products appear to be equivalent to CMV screened-negative blood products in terms of the risk of CMV transmission to a CMV-seronegative recipient.

Transfusion Graft-Versus-Host Disease

Allogeneic passenger lymphocytes in transfused blood products will engraft in some recipients and mount an alloimmune attack against tissues expressing discrepant HLA antigens causing graft-versus-host disease (GVHD). The symptoms and signs of transfusion-associated GVHD include fever, rash, diarrhea, hepatitis, lymphadenopathy, and severe pancytopenia. The outcome is usually fatal. Transfusion-associated GVHD occurs most often in recipients with immune defects, malignant lymphoproliferative disorders, solid tumors being treated with chemotherapy or immunotherapy, treatment with immunosuppressive medications (especially purine analogs such as fludarabine), or older patients undergoing cardiac surgery. HIV infection alone does not increase the risk. The use of leukoreduced blood products is inadequate to prevent transfusion-associated GVHD. This complication can be avoided by irradiating blood products (25 Gy or more) to prevent lymphocyte proliferation in blood products given to recipients at high risk for transfusion-associated GVHD.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) occurs in 1 in every 5000 transfused units of blood products. TRALI is clinically defined as noncardiogenic pulmonary edema after a blood product transfusion without other explanation. Transfused surgical and critically ill patients seem most susceptible. It has been associated with allogeneic antibodies in the donor plasma component that bind to recipient leukocyte antigens, including HLA antigens and other granulocyte- and monocyte-specific antigens (such as human neutrophil antigen [HNA]-1a, -1b, -2a, and -3a). In 20% of cases, no antileukocyte antibodies are identified raising the concern that bioactive lipids or other substances that accumulate while the blood product is in storage can also mediate TRALI in susceptible recipients. Ten to 20% of female blood donors and 1–5% of male blood donors have antileukocyte antibodies in their serum. The risk of TRALI is reduced through the use of male-only plasma donors, when possible. There is no specific treatment for TRALI, only supportive care.

PLATELET TRANSFUSIONS

Platelet transfusions are indicated in cases of thrombocytopenia due to decreased platelet production. They are of some use in immune thrombocytopenia when active bleeding is evident, but the clearance of transfused platelets is rapid as they are exposed to the same pathophysiologic forces experienced by the recipient's endogenous platelets. The risk of bleeding rises when the platelet count falls to less than 80,000/mcL (80×10^9/L), and the risk of life-threatening spontaneous bleeding increases when the platelet count is less than 5000/mcL (5×10^9/L). Because of this, prophylactic platelet transfusions are often given at these very low levels, usually when less than 10,000/mcL (10×10^9/L). Platelet transfusions are also given prior to invasive procedures or surgery in thrombocytopenic patients, and the goal is often to raise the platelet count to 50,000/mcL (50×10^9/L) or more.

Platelets for transfusion are most commonly derived from single-donor apheresis collections (roughly the equivalent to the platelets recovered from six donations of whole blood). A single donor unit of platelets should raise the platelet count by 50,000 to 60,000 platelets per mcL

($50–60 \times 10^9$/L) in a transfusion-naïve recipient without hypersplenism or ongoing platelet consumptive disorder. Transfused platelets typically last for 2 or 3 days. Platelet transfusion responses may be suboptimal with poor platelet increments and short platelet survival times. This may be due to one of several causes, including fever, sepsis, hypersplenism, DIC, large body habitus, low platelet dose in the transfusion, or platelet alloimmunization (from prior transfusions, prior pregnancy, or prior organ transplantation). Many, but not all, alloantibodies causing platelet destruction are directed at HLA antigens. Patients requiring long periods of platelet transfusion support should be monitored to document adequate responses to transfusions so that the most appropriate product can be used. If random platelet transfusions prove inadequate, then the patient should be cross-matched with potential donors who might prove better able to provide adequate platelet-transfusion increments and platelet survival. Patients requiring ongoing platelet transfusions who become alloimmunized may benefit from HLA-matched platelets derived from either volunteer donors or family members.

TRANSFUSION OF PLASMA COMPONENTS

Fresh frozen plasma (FFP) is available in units of approximately 200 mL. FFP contains normal levels of all coagulation factors (about 1 unit/mL of each factor). FFP is used to correct coagulation factor deficiencies (such as in liver disease) and to treat thrombotic thrombocytopenic purpura or other thrombotic microangiopathies. FFP is also used to correct or prevent coagulopathy in trauma patients receiving massive transfusion of packed RBC (PRBC). An FFP:PRBC ratio of 1:2 or more is associated with improved survival in trauma patients receiving massive transfusions, regardless of the presence of a coagulopathy.

Cryoprecipitate is made from fresh plasma by cooling the plasma to 4°C and collecting the precipitate. One unit of cryoprecipitate has a volume of approximately 15–20 mL and contains approximately 250 mg of fibrinogen and between 80 and 100 units of factor VIII and von Willebrand factor. Cryoprecipitate is most commonly used to supplement fibrinogen in cases of acquired hypofibrinogenemia (eg, acute DIC) or in rare instances of congenital hypofibrinogenemia. One unit of cryoprecipitate will raise the fibrinogen level by about 8 mg/dL (0.24 mcmol/L). Cryoprecipitate is sometimes used to temporarily correct the acquired qualitative platelet dysfunction associated with kidney disease.

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14 Disorders of Hemostasis, Thrombosis, & Antithrombotic Therapy

Andrew D. Leavitt, MD
Erika Leemann Price, MD, MPH

To evaluate patients for defects of hemostasis, the clinical context must be considered carefully (Table 14–1). **Heritable defects** are suggested by bleeding that begins in infancy or childhood, is recurrent, and occurs at multiple anatomic sites, although other patterns of presentation are possible. **Acquired disorders** of hemostasis typically are associated with bleeding that begins later in life and may relate to introduction of medications (eg, agents that affect platelet activity) or to onset of underlying medical conditions (such as kidney disease, liver disease, myelodysplasia, aortic stenosis, prosthetic aortic valve, myeloproliferative neoplasms, plasma cell disorders), or may be idiopathic (acquired hemophilia A, acquired von Willebrand disease). Importantly, however, a sufficient hemostatic challenge (such as major trauma) may produce excessive bleeding even in individuals with normal hemostasis. Obtaining a personal history of hemostatic challenges (eg, circumcision, trauma, injury during youth sports, tooth extractions, prior surgery, pregnancy and delivery) and a family history of bleeding are essential when evaluating someone for a possible bleeding disorder.

PLATELET DISORDERS

THROMBOCYTOPENIA

Selected causes of thrombocytopenia are shown in Table 14–2. The age of the patient and presence of comorbid conditions can help direct the diagnostic workup.

The risk of clinically relevant spontaneous bleeding (including petechial hemorrhage and bruising) does not typically increase appreciably until the platelet count falls below 10,000–20,000/mcL ($10–20 \times 10^9$/L), although patients with dysfunctional platelets or local vascular defects can bleed with higher platelet counts. Suggested platelet counts to prevent spontaneous bleeding or to provide adequate hemostasis around the time of invasive procedures are found in Table 14–3. However, most medical centers develop their own local guidelines to have a consistent approach to such complex situations.

DECREASED PLATELET PRODUCTION

1. Bone Marrow Failure

ESSENTIALS OF DIAGNOSIS

- Determine if bone marrow failure is congenital or acquired.
- Most congenital marrow failure disorders present in childhood.

General Considerations

Congenital conditions that cause thrombocytopenia include amegakaryocytic thrombocytopenia, the thrombocytopenia-absent radius syndrome, and Wiskott-Aldrich syndrome; these disorders usually feature isolated thrombocytopenia, whereas patients with Fanconi anemia and dyskeratosis congenita typically include cytopenias in other blood cell lineages. Mutations in genes (*FLI1, MYH9, GATA1, ETV6*, among others) that cause thrombocytopenia are being identified.

Acquired causes of bone marrow failure (see Chapter 13) leading to thrombocytopenia include, but are not limited to, acquired aplastic anemia, myelodysplastic syndrome (MDS), acquired amegakaryocytic thrombocytopenia (albeit a rare disorder), alcohol, and drugs. Unlike aplastic anemia, MDS is more common among older patients.

Clinical Findings

See Chapter 13 for symptoms and signs of aplastic anemia. Acquired aplastic anemia typically presents with reductions in multiple blood cell lineages, and the CBC reveals pancytopenia (anemia, thrombocytopenia, and neutropenia). A bone marrow biopsy is required for diagnosis and reveals marked hypocellularity. MDS also presents as cytopenias and can have pancytopenia, but the marrow typically demonstrates hypercellularity and dysplastic features. The presence of macrocytosis, ringed sideroblasts on iron

Table 14–1. Evaluation of the bleeding patient.

Necessary Component of Evaluation	Diagnostic Correlate
Location	
Mucocutaneous (bruises, petechiae, gingivae, nosebleeds, GI, GU)	Suggests qualitative/quantitative platelet defects; vWD
Joints, soft tissue	Suggests disorders of coagulation factors
Onset	
Infancy/childhood	Suggests heritable condition
Adulthood	Suggests milder heritable condition or acquired defect of hemostasis (eg, ITP, medication, acquired factor VIII deficiency; acquired vWD)
Clinical Context	
Postsurgical	Anatomic/surgical defect must be ruled out
Pregnancy	vWD, HELLP syndrome, ITP, acquired factor VIII inhibitor
Sepsis	May indicate DIC
Exposure to anticoagulants	Rule out excessive anticoagulation
Personal History[1]	
Absent	Suggests acquired rather than congenital defect, or anatomic/surgical defect (if applicable)
Present	Suggests established acquired defect or congenital disorder
Family History	
Absent	Suggests acquired defect or no defect of hemostasis
Present	May signify hemophilia A or B, vWD, other heritable bleeding disorders

[1]Prior spontaneous bleeding and excessive bleeding with circumcision, menses, dental extractions, trauma, minor procedures (eg, endoscopy, biopsies), and major procedures (surgery).
DIC, disseminated intravascular coagulation; GU, genitourinary; HELLP, hemolysis, elevated liver enzymes, low platelets; ITP, immune thrombocytopenia; vWD, von Willebrand disease.

staining of the bone marrow aspirate, dysplasia of hematopoietic elements, or cytogenetic abnormalities (especially monosomy 5 or 7 and trisomy 8) is more suggestive of MDS.

Differential Diagnosis

Adult patients with acquired amegakaryocytic thrombocytopenia (rare) have isolated thrombocytopenia and reduced or absent megakaryocytes in the bone marrow, which along with failure to respond to immunomodulatory regimens typically administered in immune thrombocytopenia (ITP), distinguishes them from patients with ITP.

Table 14–2. Selected causes of thrombocytopenia.

- **Decreased production of platelets**
  - Congenital bone marrow failure
    - Amegakaryocytic thrombocytopenia, Wiskott-Aldrich syndrome, Fanconi anemia
  - Acquired bone marrow failure
    - Aplastic anemia, myelodysplastic syndrome, leukemia
    - Exposure to chemotherapy, irradiation, medications (https://ouhsc.edu/platelets/ditp.html)
    - Marrow infiltration (neoplastic, infectious)
    - Nutritional (deficiency of vitamin B_{12}, folate)
    - Other: HIV, alcohol
  - Other inherited thrombocytopenias
    - Bernard-Soulier syndrome, gray platelet syndrome, May-Hegglin anomaly, Hemansky Pudlak syndrome, MYH9 mutations, and others
- **Increased destruction of platelets**
  - Immune thrombocytopenia (primary)
  - Immune thrombocytopenia (secondary), including drug-induced, lymphoproliferative disorders (eg, CLL) or viral infections (eg, hepatitis C virus, Epstein-Barr virus, or HIV)
  - Heparin-induced thrombocytopenia
  - Thrombotic microangiopathy/microangiopathic hemolytic anemias
  - Disseminated intravascular coagulation
  - Posttransfusion purpura
  - Mechanical (aortic valvular dysfunction; extracorporeal bypass)
  - von Willebrand disease, type 2B
  - Hemophagocytosis
- **Increased sequestration of platelets**
  - Hypersplenism (eg, cirrhosis, myeloproliferative disorders, lymphoma)
- **Other conditions causing thrombocytopenia**
  - Gestational thrombocytopenia
  - Pseudothrombocytopenia

CLL, chronic lymphocytic leukemia.

Treatment

A. Congenital Conditions

Treatment is varied but may include blood product support, blood cell growth factors, androgens and, in some cases, allogeneic hematopoietic stem cell transplantation.

Table 14–3. Desired platelet count ranges.

Clinical Scenario	Platelet Count /mcL (× 10^9/L)
Prevention of spontaneous mucocutaneous bleeding	> 10,000–20,000 (> 10–20)
Insertion of central venous catheters	> 20,000–50,000[1] (> 20–50)
Administration of therapeutic anticoagulation	> 30,000–50,000 (> 30–50)
Minor surgery and selected invasive procedures[2]	> 50,000–80,000 (> 50–80)
Major surgery	> 80,000–100,000 (> 80–100)

[1]A platelet target within the higher reference range is required for tunneled catheters.
[2]Such as endoscopy with biopsy.

B. Acquired Conditions

Patients with severe aplastic anemia are treated with immunosuppressive therapy or allogeneic hematopoietic stem cell transplantation (see Chapter 13).

Treatment of thrombocytopenia due to MDS, if clinically significant bleeding is present or if the risk of bleeding is high, is limited to chronic transfusion of platelets in most instances (Table 14–3). Additional treatment is discussed in Chapter 13.

Nurden AT et al. Inherited thrombocytopenias: history, advances and perspectives. Haematologica. 2020;105:2004. [PMID: 32527953]

2. Bone Marrow Infiltration

Replacement of the normal bone marrow elements by leukemic cells, plasma cell myeloma, lymphoma, or nonhematologic tumors or by infections (such as mycobacterial disease or ehrlichiosis) may cause thrombocytopenia; however, abnormalities in other blood cell lines are usually present. These entities are easily diagnosed after examining the bone marrow biopsy and aspirate or determining the infecting organism from an aspirate specimen, and they often lead to a leukoerythroblastic peripheral blood smear (left-shifted myeloid lineage cells, nucleated RBCs, and teardrop-shaped RBCs). Treatment of thrombocytopenia is directed at eradication of the underlying infiltrative disorder, but platelet transfusion may be required if clinically significant bleeding is present.

3. Chemotherapy & Irradiation

Chemotherapeutic agents and irradiation may lead to thrombocytopenia by direct toxicity to megakaryocytes, hematopoietic progenitor cells, or both. The severity and duration of chemotherapy-induced depressions in the platelet count are determined by the specific agent and regimen used, although the platelet count typically resolves more slowly following a chemotherapeutic insult than does neutropenia or anemia, especially if multiple cycles of treatment have been given. Until recovery occurs, patients may be supported with transfused platelets if bleeding is present or the risk of bleeding is high (Table 14–3). Studies suggest that that platelet growth factors, such as eltrombopag and romiplostim, may help prevent chemotherapy-induced thrombocytopenia and allow patients to receive their full chemotherapy doses on schedule. Checkpoint inhibitors can also lead to thrombocytopenia that mimics immune thrombocytopenic purpura.

Soff GA et al. Romiplostim treatment of chemotherapy-induced thrombocytopenia. J Clin Oncol. 2019;37:2892. [PMID: 31545663]

Wang Z et al. Recombinant human thrombopoietin (rh-TPO) for the prevention of severe thrombocytopenia induced by high-dose cytarabine: a prospective, randomized, self-controlled study. Leuk Lymphoma. 2018;59:2821. [PMID: 29909708]

4. Nutritional Deficiencies

Thrombocytopenia, typically in concert with anemia, may be observed with a deficiency of folate (that may accompany alcohol use disorder) or vitamin B_{12} (concomitant neurologic findings may be manifest). In addition, thrombocytopenia can occur in very severe iron deficiency, albeit rarely, whereas thrombocytosis is far more common. Replacing the deficient vitamin or mineral results in improvement in the platelet count.

5. Cyclic Thrombocytopenia

Cyclic thrombocytopenia is a rare disorder that produces cyclic oscillations of the platelet count, usually with a periodicity of 3–6 weeks. The pathophysiologic mechanism responsible for the condition is unclear. Severe thrombocytopenia and bleeding typically occur at the platelet nadir. Oral contraceptive medications, androgens, azathioprine, and thrombopoietic growth factors have been used successfully in the management of cyclic thrombocytopenia.

INCREASED PLATELET DESTRUCTION

1. Immune Thrombocytopenia

ESSENTIALS OF DIAGNOSIS

- Isolated thrombocytopenia (rule out pseudothrombocytopenia by review of peripheral smear).
- Assess for any new causative medications and HIV, hepatitis B, hepatitis C, and *Helicobacter pylori* infections.
- Immune thrombocytopenia (ITP) is a diagnosis of exclusion.

General Considerations

ITP is an autoimmune condition in which pathogenic antibodies bind platelets, accelerating their clearance from the circulation; additional pathophysiologic mechanisms include a role for T cells. Many patients with ITP also lack appropriate compensatory platelet production, thought, at least in part, to reflect the antibody's effect on megakaryocytopoiesis and thrombopoiesis. ITP is primary (idiopathic) in most adult patients, although it can be secondary (ie, associated with autoimmune disease, such as SLE; lymphoproliferative disease, such as lymphoma; medications; and infections caused by hepatitis C virus, HIV, and *H pylori*), and ITP can be exacerbated by SARS-CoV-2 vaccination. Antiplatelet antibody targets include glycoproteins IIb/IIIa and Ib/IX on the platelet membrane, although antibodies are demonstrable in only two-thirds of patients; testing for such antibodies is not standard of care given the significant false-positive and false-negative results. In addition to production of antiplatelet antibodies, HIV and hepatitis C virus may lead to thrombocytopenia

through additional mechanisms (for instance, by direct suppression of platelet production [HIV] and cirrhosis-related decreased thrombopoietin [TPO] production and secondary splenomegaly [hepatitis C virus]).

Lee EJ...Leavitt AD et al. SARS-CoV-2 vaccination and immune thrombocytopenia in de novo and pre-existing ITP patients. Blood. 2022;139:1564. [PMID: 34587251]

Clinical Findings

A. Symptoms and Signs

Mucocutaneous bleeding may be present, depending on the platelet count. Clinically relevant spontaneous bruising, epistaxis, gingival bleeding, or other types of hemorrhage generally do not occur until the platelet count has fallen below 10,000–20,000/mcL (10–20 × 10^9/L). Individuals with secondary ITP (such as due to autoimmune disease, HIV or HCV infection, SLE, or lymphoproliferative malignancy) may have additional disease-specific findings.

B. Laboratory Findings

Typically, patients have isolated thrombocytopenia. If substantial bleeding has occurred, anemia may also be present. Hepatitis B and C viruses and HIV infections should be excluded by serologic testing. *H pylori* infections can sometimes cause isolated thrombocytopenia.

Bone marrow should be examined in patients with unexplained cytopenias in two or more lineages, in patients older than 40 years with isolated thrombocytopenia, or in those who do not respond to primary ITP-specific therapy. A bone marrow biopsy is not necessary in all cases to make an ITP diagnosis in younger patients. Megakaryocyte morphologic abnormalities and hypocellularity or hypercellularity are not characteristic of ITP. ITP patients often have increased numbers of bone marrow megakaryocytes. If there are clinical findings suggestive of a lymphoproliferative malignancy, a CT scan should be performed. In the absence of such findings, otherwise asymptomatic patients younger than 40 years lacking the above infections and with unexplained isolated thrombocytopenia of recent onset may be considered to have ITP.

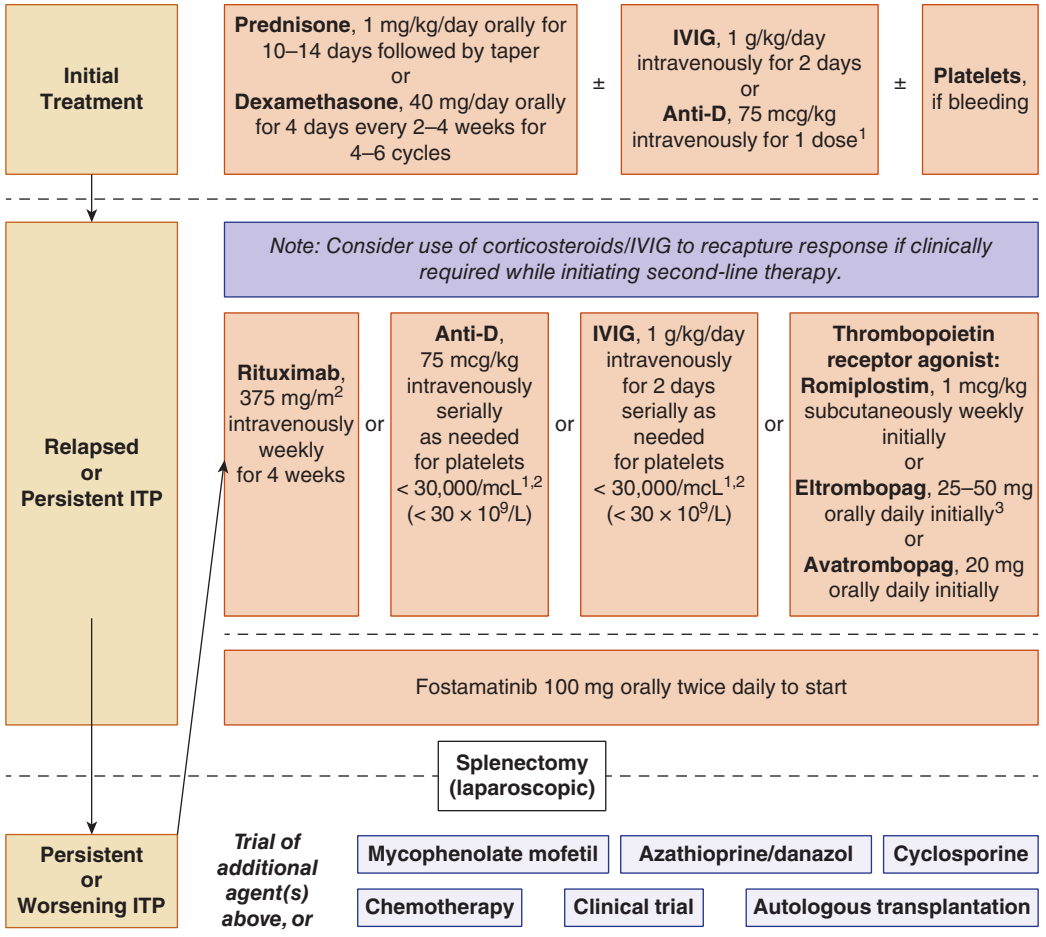
Treatment

Individuals with platelet counts less than 25,000–30,000/mcL (25–30 × 10^9/L) or those with significant bleeding should be treated; the remainder may be monitored serially for progression, but that is a patient-specific decision. The mainstay of initial treatment of new-onset primary ITP is a short course of prednisone with or without intravenous immunoglobulin (IVIG) or anti-D (WinRho) (Figure 14–1). A short course of high-dose dexamethasone is also an option for initial treatment. Response to corticosteroids is generally seen within 3–7 days of initiating treatment, with response to IVIG typically seen in 24–36 hours. Platelet transfusions may be given concomitantly if active bleeding is present. Adding the anti-B-cell monoclonal antibody rituximab to corticosteroids as first-line treatment may improve the initial response rate, but it is associated with increased toxicity and is not regarded as standard first-line therapy in most centers.

Although over two-thirds of patients with ITP respond to initial treatment with oral corticosteroids, most relapse following reduction of the corticosteroid dose. Patients with a persistent platelet count less than 30,000/mcL (30 × 10^9/L) or clinically significant bleeding are appropriate candidates for second-line treatments (Figure 14–1). These treatments are chosen empirically, bearing in mind potential toxicities and patient preference. IVIG or anti-D (WinRho) temporarily increases platelet counts (duration, up to 3 weeks, rarely longer). Serial IVIG or anti-D treatment is an option for some adult patients while alternate safe treatment is pursued. Rituximab leads to clinical responses in about 50% of adults with corticosteroid-refractory chronic ITP, which decreases to about 20% at 5 years. The TPO-mimetics romiplostim (administered subcutaneously weekly), eltrombopag (taken orally daily), and avatrombopag (taken orally daily) are used in adult patients with chronic ITP who have not responded durably to corticosteroids or IVIG. Romiplostim, eltrombopag, or avatrombopag can be taken indefinitely to maintain the platelet response and can be used as second-line therapy, but many patients can discontinue taking these agents and maintain an adequate platelet count (above 30,000/mcL [30 × 10^9/L]). The Syk inhibitor fostamatinib treats patients with ITP who do not respond to corticosteroids, TPO-mimetics, or rituximab. Splenectomy is now used infrequently; it has a durable response rate of over 50% and may be considered for cases of severe ITP that fail to respond durably to initial treatment or are refractory to second-line agents; patients should receive pneumococcal, *Haemophilus influenzae* type b, and meningococcal vaccination at least 2 weeks before therapeutic splenectomy. If available, laparoscopic splenectomy is preferred. Additional treatments for ITP are found in Figure 14–1.

For thrombocytopenia associated with HIV or hepatitis C virus, effective treatment of either infection leads to an amelioration of thrombocytopenia in most cases; refractory thrombocytopenia may require the use of IVIG, splenectomy, TPO-mimetic, or anti-CD20 therapy. Occasionally, ITP treatment response is impaired due to *H pylori* infection, which should be ruled out in the appropriate situation.

Management goals for **pregnancy-associated ITP** are a platelet count of 10,000–30,000/mcL (10–30 × 10^9/L) in the first trimester, greater than or equal to 30,000/mcL (30 × 10^9/L) during the second or third trimester, and greater than 50,000/mcL (50 × 10^9/L) prior to cesarean section or vaginal delivery. Moderate-dose oral prednisone or intermittent IVIG infusions are standard treatment options. Splenectomy is reserved for failure to respond to these therapies and may be performed in the first or second trimester. Management requires close interaction between obstetrician and hematologist. TPO-mimetics are not approved for use during pregnancy.



[1]Use in non-splenectomized, Rh blood type–positive, non-anemic patients only.
[2]May need to repeat infusion every 2–6 weeks to maintain platelet response.
[3]Recommended starting dose in Asian patients is 25 mg daily.

▲ **Figure 14–1.** Management of immune thrombocytopenia (ITP), a simplified overview.

When to Refer

All patients with ITP need to be managed by a hematologist because of the complexity of the decision making.

When to Admit

Patients with major hemorrhage or severe thrombocytopenia associated with bleeding should be admitted and monitored in-hospital until the platelet count has consistently risen to more than 20,000–30,000/mcL (20–30 × 10^9/L) and hemodynamic stability has been achieved.

Bussel J et al. Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: results of two phase 3, randomized, placebo-controlled trials. Am J Hematol. 2018;93:921. [PMID: 29696684]
Miltiadous O et al. Identifying and treating refractory ITP: difficulty in diagnosis and role of combination treatment. Blood. 2020;135:472. [PMID: 31756253]
Neunert C et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3:3829. [PMID: 31794604]

2. Thrombotic Microangiopathy

ESSENTIALS OF DIAGNOSIS

- Microangiopathic hemolytic anemia and thrombocytopenia, without another plausible explanation, are sufficient for a presumptive diagnosis of thrombotic microangiopathy (TMA).
- Fever, neurologic impairment, and kidney disease may occur but are not required for diagnosis.
- Kidney injury is more common and more severe in hemolytic-uremic syndrome (HUS).

General Considerations

The TMAs include, but are not limited to, thrombotic thrombocytopenic purpura (TTP) and HUS. These disorders are characterized by thrombocytopenia due to the incorporation of platelets into fibrin thrombi in

the microvasculature, and microangiopathic hemolytic anemia, which results from shearing of erythrocytes in fibrin networks in the microcirculation.

In idiopathic TTP, autoantibodies against ADAMTS-13 (a disintegrin and metalloproteinase with thrombospondin type 1 repeat, member 13), also known as the von Willebrand factor (vWF) cleaving protease (vWFCP), lead to accumulation of ultra-large vWF multimers. The ultra-large multimers bridge and aggregate platelets in the absence of hemostatic triggers, which in turn leads to the vessel obstruction and various organ dysfunctions seen in TTP. In some cases of pregnancy-associated TMA, an antibody to ADAMTS-13 is present. In contrast, the activity of the ADAMTS-13 in congenital TTP is decreased due to a mutation in the gene encoding the molecule. Classic HUS, called Shiga toxin–mediated HUS, is thought to be secondary to toxin-mediated endothelial damage and is often contracted through the ingestion of undercooked ground beef contaminated with *Escherichia coli* (especially types O157:H7 or O145).

Complement-mediated HUS (formerly called atypical HUS) is not related to Shiga toxin. Patients with complement-mediated HUS often have genetic defects in proteins that regulate complement activity. Damage to endothelial cells, hematopoietic stem cell transplantation in the setting of cancer, or HIV infection may also lead to TMA. Certain medications (eg, cyclosporine, quinine, ticlopidine, clopidogrel, mitomycin C, and bleomycin) are associated with the development of TMA, possibly by promoting injury to endothelial cells, although inhibitory antibodies to ADAMTS-13 have been demonstrated in some cases.

Clinical Findings

A. Symptoms and Signs

Microangiopathic hemolytic anemia and thrombocytopenia are presenting signs in all patients with TTP and most patients with HUS; in a subset of patients with HUS, the platelet count remains in the normal range. Only about 25% of patients with TTP manifest all components of the original pentad of findings (microangiopathic hemolytic anemia, thrombocytopenia, fever, kidney disease, and neurologic abnormalities) (Table 14–4). Most patients (especially children) with HUS have a recent or current diarrheal illness, often bloody. Neurologic manifestations, including headache, somnolence, delirium, seizures, paresis, and coma, may result from deposition of microthrombi in the cerebral vasculature.

B. Laboratory Findings

Laboratory features of TMA include those associated with microangiopathic hemolytic anemia (anemia, elevated LD, elevated indirect bilirubin, decreased haptoglobin, schistocytes on the blood smear, elevated reticulocyte count, and a negative direct antiglobulin test); thrombocytopenia; elevated creatinine; positive stool culture for *E coli* O157:H7 or stool assays for Shiga toxin; reductions in ADAMTS-13 activity with the presence (acquired TTP) or absence (inherited TTP) of ADAMTS-13 inhibitor; and mutations of genes encoding complement proteins (complement-mediated HUS; specialized laboratory assessment). Routine coagulation studies (prothrombin time [PT], activated

Table 14–4. Presentation and management of thrombotic microangiopathies.

	TTP	Complement-Mediated HUS	Shiga Toxin–Mediated HUS
Patient population	Adults	Children (occasionally adults)	Usually children, often following bloody diarrhea
Pathogenesis	Acquired autoantibody to ADAMTS-13	Some cases: heritable deficiency in function of complement regulatory proteins	Bacterial (such as enterotoxogenic *Escherichia coli;* Shiga toxin)
Thrombocytopenia	Typically severe, except in very early clinical course	Variable	May be mild/absent in a minority of patients
Fever	Typical	Variable	Atypical
Kidney disease	Typical, but may be mild	Typical	Typical
Neurologic impairment	Variable	Less than half of cases	Less than half of cases
Laboratory investigation	Decreased activity of ADAMTS-13; inhibitor usually identified	Defects in complement regulatory proteins	Typically normal ADAMTS-13 activity Positive stool culture for *E coli* 0157:H7 or detectable antibody to Shiga toxin
Management	Immediate TPE in most cases Hemodialysis for severe kidney disease Caplacizumab (selected patients) Platelet transfusions contraindicated unless TPE underway	Immediate TPE initially in most cases Eculizumab Supportive care Hemodialysis for severe kidney disease	Hemodialysis for severe kidney disease Supportive care TPE rarely beneficial (exception: selected cases in adults)

ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; HUS, hemolytic-uremic syndrome; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura.

partial thromboplastin time [aPTT], fibrinogen) are within the normal range in most patients with TTP or HUS.

Treatment

With the exception of children or adults with endemic diarrhea-associated HUS, who generally recover with supportive care only, plasma exchange must be initiated as soon as the diagnosis of TMA is suspected and in all cases of TTP. *Immediate administration of plasma exchange is essential in most cases of TTP because the mortality rate without treatment is over 95%.* Plasma exchange usually is administered once daily until the platelet count and LD have returned to normal for at least 2 days, after which the frequency of treatments may be tapered or stopped while the platelet count and LD are monitored for relapse. In cases of insufficient response to once-daily plasma exchange, twice-daily treatments can be considered. Fresh frozen plasma (FFP) may be administered if immediate access to plasma exchange is not available or in cases of familial TMA. *Platelet transfusions are contraindicated* in the treatment of TMA due to reports of worsening TMA, possibly due to propagation of platelet-rich microthrombi. In cases of documented life-threatening bleeding, however, platelet transfusions may be given slowly and preferably after plasma exchange is underway. RBC transfusions may be administered in cases of clinically significant anemia. Hemodialysis should be considered for patients with significant kidney injury. Caplacizumab, a bi-specific antibody that targets the A1 domain of vWF and prevents vWF interaction with the platelet glycoprotein Ib-IX-V receptor, can reduce the time to platelet count normalization and 30-day mortality. The role of caplacizumab in the treatment of TTP remains controversial given its high cost and limited benefit, despite its inclusion in 2020 guidelines.

In cases of TTP relapse following initial treatment, plasma exchange should be reinstituted. If ineffective, or in cases of primary refractoriness, second-line treatments including rituximab (which has shown efficacy when administered preemptively in selected cases of relapsing TTP), corticosteroids, IVIG, vincristine, cyclophosphamide, and splenectomy should be used. Idiopathic TTP is a relapsing autoimmune disorder (antibody inhibitor to ADAMTS-13) for most patients; careful monitoring of the ADAMTS-13 activity and inhibitor status and use of rituximab can prevent dangerous relapses.

Complement-mediated HUS may respond to plasma infusion initially; however, once this diagnosis is strongly suspected, apheresis is typically stopped and serial infusions of the anti-complement C5 antibody eculizumab are given, which have produced sustained remissions in some patients. Hemodialysis or kidney transplantation may be necessary for irreversible kidney injury.

When to Refer

Consultation by a hematologist or transfusion medicine specialist familiar with plasma exchange is required at the time of presentation. Patients with TMA and TTP require ongoing care by a hematologist.

When to Admit

All patients with newly suspected or diagnosed TMA should be hospitalized immediately.

Goshua G et al. Cost effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. Blood. 2021;137:969. [PMID: 33280030]
Scully M et al; HERCULES Investigators. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2019;380:335. [PMID: 30625070]
Zheng XL et al. ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020;18:2486. [PMID: 32914582]
Zheng XL et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020;18:2496. [PMID: 32914526]

3. Heparin-Induced Thrombocytopenia

ESSENTIALS OF DIAGNOSIS

- Thrombocytopenia within 5–14 days of exposure to heparin.
- Decline in baseline platelet count of ≥ 50%.
- Thrombosis occurs in up to 50% of cases; bleeding is uncommon.

General Considerations

Heparin-induced thrombocytopenia (HIT) is an acquired disorder that affects approximately 3% of patients exposed to unfractionated heparin and ~0.3–0.6% of patients exposed to low-molecular-weight heparin (LMWH). The condition results from formation of IgG antibodies to heparin-platelet factor 4 (PF4) complexes; the antibody:heparin-PF4 complex binds to and activates platelets independent of physiologic hemostasis, which leads to thrombocytopenia and thromboses. von Willebrand factor has been postulated to play a role in the thrombotic events that take place long after heparin is cleared from the patient's system.

Clinical Findings

A. Symptoms and Signs

Patients are often asymptomatic, and due to the prothrombotic nature of HIT, bleeding usually does not occur. Thrombosis (at any venous or arterial site), however, may be detected in up to 50% of patients, up to 30 days post diagnosis. If thrombosis has not already been detected, the use of duplex Doppler ultrasound of the lower extremities should be considered to rule out subclinical DVT.

B. Laboratory Findings

A presumptive diagnosis of HIT is made when new-onset thrombocytopenia is detected in a patient (typically a hospitalized patient) within 5–14 days of initial exposure to heparin; other presentations (eg, rapid-onset HIT) are less

common and reflect recent prior heparin exposure. A decline of 50% or more from the baseline platelet count is typical. The 4T score (http://www.qxmd.com/calculate-online/hematology/hit-heparin-induced-thrombocytopenia-probability) is a clinical prediction rule for assessing pretest probability for HIT. Low 4T scores have been shown to be more predictive of excluding HIT than are intermediate or high scores of predicting its presence. Once HIT is clinically suspected, the clinician must establish the diagnosis by performing a screening PF4-heparin antibody ELISA. If the PF4-heparin antibody ELISA is positive, the diagnosis must be confirmed using a functional assay (such as serotonin release assay). The magnitude of a positive ELISA result correlates with the clinical probability of HIT, but even high ELISA optical density values may be falsely positive. The confirmatory functional assay is essential.

Treatment

Treatment should be initiated as soon as the diagnosis of HIT is suspected, before laboratory test results are available.

Management of HIT (Table 14–5) involves the immediate discontinuation of all forms of heparin. Despite thrombocytopenia, platelet transfusions are rarely necessary and should be avoided. Due to the substantial frequency of thrombosis among HIT patients, an alternative anticoagulant should be administered immediately while awaiting confirmatory testing. A direct thrombin inhibitor (DTI), such as argatroban or bivalirudin, is preferred in critical illness because of the shorter duration of action. The use of the subcutaneous indirect anti-Xa inhibitor fondaparinux for initial treatment of HIT is a reasonable option in clinically stable patients. For confirmed HIT, the DTI should be continued until the platelet count has recovered to at least 100,000/mcL (100×10^9/L), at which point treatment with a vitamin K antagonist (warfarin) may be initiated. The DTI should be continued until therapeutic anticoagulation with the vitamin K antagonist warfarin has been achieved (ie, INR of 2.0–3.0); the infusion of argatroban must be temporarily discontinued before the INR is obtained so that it reflects the anticoagulant effect of warfarin alone. There is a growing use of oral anti-Xa agents instead of vitamin K antagonists in selected patients. In all patients with HIT, some form of anticoagulation (warfarin, fondaparinux, or an oral anti-Xa agent) should be continued for at least 30 days, due to a persistent risk of thrombosis even after the platelet count has recovered, but in patients in whom thrombosis has been documented, anticoagulation should continue for 3–6 months.

Subsequent exposure to heparin should be avoided in all patients with a prior history of HIT, if possible. If its use is regarded as necessary for a procedure, it should be withheld until PF4-heparin antibodies are no longer detectable by ELISA (usually as of 100 days following an episode of HIT), and exposure should be limited to the shortest time period possible. A common example is a cardiac catheterization. The heparin is gone before the antibody returns, so HIT is avoided.

Table 14–5. Management of suspected or proven HIT.

I. Discontinue all forms of heparin. Send PF4-heparin ELISA. Send confirmatory serotonin release assay if positive ELISA.		
II. Begin treatment with direct thrombin inhibitor, or in some circumstances, fondaparinux.		
Agent	**Indication**	**Dosing**
Argatroban	Prophylaxis or treatment of HIT	Continuous intravenous infusion of 0.5–1.2 mcg/kg/minute, titrate to aPTT = 1.5 to 3 × the baseline value.[1] Max infusion rate is 10 mcg/kg/minute.
Bivalirudin	Percutaneous coronary intervention[2]	Bolus of 0.75 mg/kg intravenously followed by initial continuous intravenous infusion of 1.75 mg/kg/hour. Manufacturer indicates monitoring should be by ACT.
Fondaparinux	Treatment of HIT	5–10 mg (weight based)
III. Perform Doppler ultrasound of lower extremities to rule out subclinical thrombosis (if indicated).		
IV. Follow platelet counts daily until recovery occurs.		
V. When platelet count has recovered, transition anticoagulation to warfarin, fondaparinux, or an oral anti-Xa agent; treat for 30 days (HIT) or 3–6 months (HITT).		
VI. Document heparin allergy in medical record (confirmed cases).		

[1]Liver insufficiency: initial infusion rate = 0.5 mcg/kg/minute.
[2]Not approved for HIT/HITT.
ACT, activated clotting time; aPTT, activated partial thromboplastin time; HIT, heparin-induced thrombocytopenia; HITT, heparin-induced thrombocytopenia and thrombosis; PF4, platelet factor 4.

When to Refer

Due to the tremendous thrombotic potential of the disorder and the complexity of use of the DTI, all patients with HIT should be evaluated by a hematologist.

When to Admit

Most patients with HIT are hospitalized at the time of detection of thrombocytopenia. Admission is a clinical decision for an outpatient in whom HIT is suspected and who is a candidate for subcutaneous fondaparinux or an oral anti-Xa agent. Other outpatients may need admission for intravenous DTIs. Regardless, a hematologist needs to be involved as soon as the diagnosis is suspected or treatment is indicated.

Cuker A et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2:3360. [PMID: 30482768]
Johnston I et al. Recognition of PF4-VWF complexes by heparin-induced thrombocytopenia antibodies contributes to thrombus propagation. Blood. 2020;135:1270. [PMID: 32077913]
Warkentin TE. Laboratory diagnosis of heparin-induced thrombocytopenia. Int J Lab Hematol. 2019;41:15. [PMID: 31069988]

4. Disseminated Intravascular Coagulation

ESSENTIALS OF DIAGNOSIS

- Associated with cancer, sepsis, trauma, and obstetrical patients.
- Prolonged PT and aPTT, and low/declining fibrinogen.
- Thrombocytopenia.

General Considerations

Disseminated intravascular coagulation (DIC) is caused by uncontrolled local or systemic activation of coagulation, which leads to depletion of coagulation factors and fibrinogen, and often results in thrombocytopenia as platelets are activated and consumed.

Numerous disorders are associated with DIC, including sepsis (in which coagulation is activated by presence of lipopolysaccharide), cancer, trauma, burns, and pregnancy-associated complications (in which tissue factor is released). Aortic aneurysm and cavernous hemangiomas may promote localized intravascular coagulation, and snake bites may result in DIC due to the introduction of exogenous toxins.

Clinical Findings

A. Symptoms and Signs

Bleeding in DIC usually occurs at multiple sites, such as at intravenous catheters or incisions, and may be widespread (purpura fulminans). Malignancy-related DIC may manifest principally as thrombosis (Trousseau syndrome).

B. Laboratory Findings

In early DIC, the platelet count and fibrinogen levels often remain within the normal range, albeit reduced from baseline levels. There is progressive thrombocytopenia (rarely severe), prolongation of the PT, decrease in fibrinogen levels, and eventually elevation in the aPTT. D-dimer levels typically are elevated due to the activation of coagulation and diffuse cross-linking of fibrin followed by fibrinolysis. Schistocytes on the blood smear, due to shearing of red cells through the microvasculature, are present in 10–20% of patients. Laboratory abnormalities in the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), a severe form of DIC with a particularly high mortality rate that occurs in peripartum women, include elevated liver transaminases and kidney injury due to gross hemoglobinuria and pigment nephropathy. Malignancy-related DIC may initially feature normal platelet counts and coagulation studies, but clinicians often see a dropping platelet count and fibrinogen, with a rising INR, highlighting the importance of serial laboratory values to help make the diagnosis.

Treatment

The underlying causative disorder must be treated (eg, antimicrobials, chemotherapy, surgery, or delivery of conceptus). If clinically significant bleeding is present, hemostasis must be achieved (Table 14–6).

Blood products are administered if clinically significant hemorrhage has occurred or is thought likely to occur without intervention based on progressively increasing PT and PTT and decreasing fibrinogen and platelets levels (Table 14–6). The goal of platelet therapy for most cases is greater than 20,000/mcL (20×10^9/L) or greater than 50,000/mcL (50×10^9/L) for serious bleeding, such as intracranial bleeding. FFP is typically given only to patients with a prolonged aPTT and PT and significant bleeding. Cryoprecipitate may be given for bleeding or for fibrinogen levels less than 80–100 mg/dL. The clinician should correct the fibrinogen level with cryoprecipitate prior to giving FFP for prolonged PT and aPTT to see if the fibrinogen replacement alone corrects the PT and aPTT. The PT, aPTT, fibrinogen, and platelet count should be monitored at least every 6–8 hours in acutely ill patients with DIC.

In some cases of refractory bleeding despite replacement of blood products, administration of low doses of heparin can be considered. The clinician must remember that DIC is primarily a disorder of excessive clotting with secondary fibrinolysis, and that heparin can interfere with thrombin generation, which leads to less consumption of coagulation proteins and platelets. An infusion of 5 units/kg/hour (no bolus) may be used with appropriate clinical

Table 14–6. Management of DIC.

I. Assess for underlying cause of DIC and treat.	
II. Establish baseline platelet count, PT, aPTT, D-dimer, fibrinogen.	
III. Transfuse blood products only if ongoing bleeding or high risk of bleeding.	**Platelets:** goal > 20,000/mcL (20×10^9/L) (most patients) or > 50,000/mcL (50×10^9/L) (severe bleeding, eg, intracranial hemorrhage)
	Cryoprecipitate: goal fibrinogen level > 80–100 mg/dL
	Fresh frozen plasma: goal PT and aPTT < 1.5 × normal
	Packed RBCs: goal hemoglobin > 8 g/dL or improvement in symptomatic anemia
IV. Follow platelets, aPTT, PT, fibrinogen every 4–12 hours as clinically indicated.	
V. If persistent bleeding due to severe consumption or consumption that requires excessive blood product use, consider use of heparin[1] (initial infusion, 5 units/kg/hour) and titrate to desired clinical goals; do not administer bolus.	
VI. Follow laboratory parameters every 4–12 hours as clinically indicated until DIC resolves	

[1]Contraindicated if platelets cannot be maintained at > 50,000/mcL (50×10^9/L), in cases of GI or CNS bleeding, in conditions that may require surgical management, or placental abruption.
aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; PT, prothrombin time.

judgement, up-titrated as clinically indicated. *Heparin, however, can be contraindicated if the platelet count cannot be maintained above 30,000/mcL (30 × 10^9/L) and in cases of CNS hemorrhage, GI bleeding, placental abruption, and any other condition that is likely to require imminent surgery*. Fibrinolysis inhibitors may be considered in select DIC patients with bleeding, but this can promote dangerous clotting and should be undertaken with great caution and only in consultation with a hematologist.

1. HELLP syndrome—The treatment must include evacuation of the uterus (eg, delivery of a term or near-term infant or removal of retained placental or fetal fragments).

2. Trousseau syndrome—Patients require treatment of the underlying malignancy and administration of unfractionated heparin or subcutaneous therapeutic-dose LMWH as treatment of thrombosis, since warfarin typically is less effective at secondary prevention of thromboembolism in the disorder. Typically, the heparin or LMWH treatment will gradually return the fibrinogen, PT (INR), aPTT, and platelet count back to normal, but it can take many days. Oral anti-Xa agents or oral DTIs can be considered once stabilized with parenteral heparin or LMWH, but extended LMWH is often used in this setting.

Immediate initiation of medical treatment (usually within 24 hours of diagnosis) is required for acute promyelocytic leukemia (APL)–associated DIC, along with administration of blood products as clinically indicated.

When to Refer

- Diffuse bleeding unresponsive to administration of blood products should be evaluated by a hematologist.
- All patients with DIC should be cared for by a hematologist prior to starting treatment with heparin or LMWH.

When to Admit

Most patients with DIC are hospitalized when DIC is detected.

Cuker A et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2:3360. [PMID: 30482768]

Levi M et al. Disseminated intravascular coagulation: an update on pathogenesis and diagnosis. Expert Rev Hematol. 2018;11:663. [PMID: 29999440]

Levi M. Pathogenesis and diagnosis of disseminated intravascular coagulation. Int J Lab Hematol. 2018;40:15. [PMID: 29741245]

Warkentin TE et al. Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. Blood. 2017;130:1104. [PMID: 28646118]

OTHER CONDITIONS CAUSING THROMBOCYTOPENIA

1. Drug-Induced Thrombocytopenia

Drug-induced thrombocytopenia is often immune-mediated but can also be due to marrow suppression. Table 14–7 lists medications associated with thrombocytopenia. The typical presentation of drug-induced, antibody-mediated thrombocytopenia is severe thrombocytopenia and mucocutaneous bleeding 5–14 days after exposure to a new drug, although a range of presentations is possible. Discontinuation of the offending agent leads to resolution of thrombocytopenia within 3–7 days in most cases, but recovery kinetics depend on rate of drug clearance, which can be affected by liver and kidney function. Patients with severe thrombocytopenia should be given platelet transfusions with or without IVIG. The University of Oklahoma Health Sciences center maintains a useful website for drug-induced thrombocytopenia (https://www.ouhsc.edu/platelets/).

Table 14–7. Selected medications causing drug-associated thrombocytopenia.[1]

Class	Examples
Chemotherapy	Most agents
Antiplatelet agents	Abciximab, eptifibatide, tirofiban Anagrelide Ticlopidine
Antimicrobial agents	Adefovir, indinavir, ritonavir Fluconazole Isoniazid Linezolid Penicillins Remdesivir Rifampin Sulfa drugs Vancomycin
Cardiovascular agents	Amiodarone Atorvastatin, simvastatin Captopril Digoxin Hydrochlorothiazide Procainamide
GI agents	Cimetidine, famotidine
Neuropsychiatric agents	Carbamazepine Haloperidol Methyldopa Phenytoin
Analgesic agents	Acetaminophen Diclofenac, ibuprofen, naproxen, sulindac
Anticoagulant agents	Heparin Low-molecular-weight heparin
Immunomodulator agents	Interferon-alpha Rituximab
Immunosuppressant agents	Mycophenolate mofetil Tacrolimus
Other agents	Immunizations Iodinated contrast dye

[1]See also https://www.ouhsc.edu/platelets/.

2. Posttransfusion Purpura

Posttransfusion purpura (PTP) is a rare disorder of sudden-onset thrombocytopenia that occurs within 1 week

after transfusion of red cells, platelets, or plasma. Antibodies against the human platelet antigen PL^{A1} are detected in most individuals with PTP. Patients with PTP often are either multiparous women or persons who have received transfusions previously. Severe thrombocytopenia and bleeding are typical. Initial treatment consists of administration of IVIG (1 g/kg/day for 2 days), which should be administered as soon as the diagnosis is suspected. Platelets are not indicated unless severe bleeding is present, but if they are to be administered, HLA-matched PL^{A1}-negative platelets are preferred. A second course or IVIG, plasma exchange, corticosteroids, TPO-mimetics, or splenectomy may be required in case of refractoriness. PL^{A1}-negative or washed blood products are preferred for subsequent transfusions, but data supporting various treatment options are limited.

Vu K, Leavitt AD. Posttransfusion purpura with antibodies against human platelet antigen-4a following checkpoint inhibitor therapy: a case report and review of the literature. Transfusion. 2018;58:2265. [PMID: 30222869]

3. von Willebrand Disease Type 2B

von Willebrand disease (vWD) type 2B leads to chronic, characteristically mild to moderate thrombocytopenia due to an abnormal vWF molecule that binds platelets with increased affinity, resulting in aggregation and clearance (see von Willebrand Disease, below).

4. Platelet Sequestration

One-third of the platelet mass is typically sequestered in the spleen. Splenomegaly, due to a variety of conditions, may lead to thrombocytopenia of variable severity. When possible, treatment of the underlying disorder should be pursued, but splenectomy, splenic embolization, or splenic irradiation may be considered in selected cases.

5. Pregnancy

Gestational thrombocytopenia is thought to result from progressive expansion of the blood volume that typically occurs during pregnancy, leading to hemodilution. Cytopenias result even though blood cell production is normal or increased. Platelet counts less than 100,000/mcL (100×10^9/L), however, are observed in less than 10% of pregnant women in the third trimester; decreases to less than 70,000/mcL (70×10^9/L) should prompt consideration of pregnancy-related ITP as well as preeclampsia or a pregnancy-related thrombotic microangiopathy.

6. Infection or Sepsis

The exact mechanism underlying sepsis-related thrombocytopenia remains ill-defined. Immune-mediated destruction and enhanced clearance by the liver are possible explanations, and there may be significant overlap with concomitant DIC. Regardless, the platelet count typically improves with effective antimicrobial treatment or after the infection has resolved. Hemophagocytosis may occur in some critically ill patients; a defect in immunomodulation may lead to bone marrow macrophages (histiocytes) engulfing cellular components of the marrow. The phenomenon typically resolves with resolution of the infection, but with certain infections (Epstein-Barr virus) immunosuppression may be required. Hemophagocytosis also may occur with malignancy, in which case the disorder is usually unresponsive to treatment with immunosuppression and requires treatment of the malignancy.

7. Pseudothrombocytopenia

Pseudothrombocytopenia results from ethylenediaminetetraacetic acid (EDTA) anticoagulant-induced platelet clumping; the phenomenon typically disappears when blood is collected in a tube containing citrate anticoagulant. Pseudothrombocytopenia diagnosis requires review of the peripheral blood smear and is not associated with bleeding.

Ghimire S et al. Current understanding and future implications of sepsis-induced thrombocytopenia. Eur J Haematol. 2021;106:301. [PMID: 33191517]
Koyama K et al. Time course of immature platelet count and its relation to thrombocytopenia and mortality in patients with sepsis. PLoS One. 2018;13:e0192064. [PMID: 29381746]

QUALITATIVE PLATELET DISORDERS

CONGENITAL DISORDERS OF PLATELET FUNCTION

ESSENTIALS OF DIAGNOSIS

- Usually diagnosed in childhood.
- Family history usually is positive.
- May be diagnosed in adulthood when there is excessive bleeding.

General Considerations

Heritable qualitative platelet disorders are far less common than acquired platelet function disorders and lead to variably severe bleeding, often beginning in childhood. Occasionally, however, disorders of platelet function may go undetected until later in life when excessive bleeding occurs following a sufficient hemostatic challenge. Thus, the true incidence of hereditary qualitative platelet disorders is unknown.

Bernard-Soulier syndrome (BSS) is a rare, autosomal recessive bleeding disorder due to reduced or abnormal platelet membrane expression of glycoprotein Ib/IX (vWF receptor).

Glanzmann thrombasthenia results from an abnormality in the platelet glycoprotein IIb/IIIa receptor on the platelet membrane. Glycoprotein IIb/IIIa is the fibrinogen receptor critical for linking platelets during initial platelet aggregation/platelet plug formation. Inheritance is autosomal recessive.

Under normal circumstances, activated platelets release the contents of platelet granules to reinforce the aggregatory response. Storage pool disease includes a spectrum of defects in release of alpha or dense (delta) platelet granules, or both (alpha-delta storage pool disease).

Clinical Findings

A. Symptoms and Signs

Bleeding due to defective platelets is usually mucocutaneous, but it is not limited to mucocutaneous surfaces. The onset of bleeding with Glanzmann thrombasthenia is usually in infancy or childhood, but some forms are milder and present later in life. The degree of deficiency in IIb/IIIa may not correlate well with bleeding symptoms. Patients with storage pool disease are affected by variable bleeding, ranging from mild and trauma-related to spontaneous.

B. Laboratory Findings

Patients with Bernard-Soulier syndrome have abnormally large platelets (approaching the size of red cells), moderate thrombocytopenia, and a prolonged bleeding time. Platelet aggregation studies show a marked defect in response to ristocetin, whereas aggregation in response to other agonists is normal; the addition of normal platelets corrects the abnormal aggregation. The diagnosis can be confirmed by platelet flow cytometry.

In Glanzmann thrombasthenia, platelet aggregation studies show marked impairment of aggregation in response to stimulation with various agonists, which reflects the critical role of the fibrinogen receptor in platelet plug formation.

Storage pool disease includes defects in the number, content, or function of platelet alpha or dense granules, or both. The gray platelet syndrome comprises abnormalities of platelet alpha granules, thrombocytopenia, and marrow fibrosis. The blood smear shows agranular platelets, and the diagnosis is confirmed with electron microscopy.

Treatment

The mainstay of treatment (including periprocedural prophylaxis) is transfusion of normal platelets, although desmopressin acetate (DDAVP), antifibrinolytic agents, and recombinant human activated factor VII each have a role in selected clinical situations.

Orsini S et al; European Hematology Association-Scientific Working Group (EHA-SWG) on thrombocytopenias and platelet function disorders. Bleeding risk of surgery and its prevention in patients with inherited platelet disorders. Haematologica. 2017;102:1192. [PMID: 28385783]

ACQUIRED DISORDERS OF PLATELET FUNCTION

Platelet dysfunction is more commonly acquired than inherited; the widespread use of platelet-altering medications accounts for most of the cases of qualitative defects. In cases where platelet function is irreversibly altered, platelet inhibition typically recovers within 7–9 days following discontinuation of the drug, which is the time it takes to replace all of the impaired platelets with newly produced platelets. In cases where platelet function is nonirreversibly affected, platelet inhibition recovers with clearance of the drug from the system. Transfusion of platelets may be required if clinically significant bleeding is present.

Lee RH et al. Impaired hemostatic activity of healthy transfused platelets in inherited and acquired platelet disorders: mechanisms and implications. Sci Transl Med. 2019;11:eaay0203. [PMID: 31826978]

Zheng SL et al. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. JAMA. 2019;321:277. [PMID: 30667501]

DISORDERS OF COAGULATION

CONGENITAL DISORDERS OF COAGULATION

1. Hemophilia A & B

ESSENTIALS OF DIAGNOSIS

- **Hemophilia A:** congenital deficiency of coagulation factor VIII.
- **Hemophilia B:** congenital deficiency of coagulation factor IX.
- Recurrent hemarthroses and arthropathy.
- Risk of development of inhibitory antibodies to factor VIII or factor IX.
- Many older patients received blood products contaminated with HIV or hepatitis C virus.

General Considerations

Hemophilia A occurs in ~1 per 5000 live male births, whereas hemophilia B occurs in ~1 in 25,000 live male births. Inheritance is X-linked recessive for both, leading to affected males and carrier (affected) females with variable bleeding tendencies. Daughters of all affected males are obligate carriers. There is no race predilection. Factor activity testing is indicated for male infants with a hemophilic maternal pedigree who are asymptomatic or who experience excessive bleeding, for all daughters of affected males (100% chance of being affected) and carrier mothers (50% chance of being affected), and for otherwise asymptomatic adolescents or adults who experience unexpected excessive bleeding with trauma or invasive procedures.

Inhibitors to factor VIII develop in approximately 20–25% of patients with severe hemophilia A; inhibitors to factor IX develop in less than 5% of patients with severe hemophilia B. Risk of inhibitor formation exists for both plasma-derived and recombinant factor products.

A substantial proportion of older patients with hemophilia acquired infection with HIV or HCV or both in the

1980s due to exposure to contaminated factor concentrates and blood products.

Clinical Findings

A. Symptoms and Signs

Severe hemophilia (factor VIII activity less than 1%) presents in infants or in early childhood with spontaneous bleeding into joints, soft tissues, or other locations. Spontaneous bleeding is much less common in patients with mild hemophilia (factor VIII activity greater than 5%), but bleeding is common with provoked bleeding (eg, surgery, trauma). Intermediate clinical symptoms are seen in patients with moderate hemophilia (factor VIII activity 1–5%). Female carriers of hemophilia can have a wide range of factor VIII activity and therefore have variable bleeding tendencies.

Significant hemophilic arthropathy can be minimized in patients who receive long-term regular prophylaxis with factor concentrate starting in early childhood, whereas destructive joint disease is common in adults who have experienced recurrent hemarthroses. Patients tend to have one or two "target" joints into which they bleed most often.

Inhibitor development to factor VIII or factor IX is characterized by bleeding episodes that are resistant to treatment with clotting factor VIII or IX concentrate, and by new or atypical bleeding.

B. Laboratory Findings

Hemophilia A or B is diagnosed by an isolated reproducibly low factor VIII or factor IX activity level, in the absence of other conditions. If the aPTT is prolonged, it typically corrects upon mixing with normal plasma. Depending on the level of residual factor VIII or factor IX activity, and the sensitivity of the thromboplastin used in the aPTT coagulation reaction, the aPTT may or may not be prolonged, although it typically is markedly prolonged in severe hemophilia. Hemophilia is classified according to the level of factor activity in the plasma. **Mild hemophilia** has greater than 5% factor activity; **moderate hemophilia** has 1–5% factor activity; and **severe hemophilia** has less than 1% factor activity. Female carriers may become symptomatic if significant lyonization has occurred favoring the defective factor VIII or factor IX gene, leading to factor VIII or factor IX activity level markedly less than 50%. Typically, a clinical bleeding diathesis occurs once the factor activity is less than 20%, but this appears to be patient-specific, and bleeding can occur in trauma, surgery, and delivery if the factor activity is less than 50%.

In the presence of an inhibitor to factor VIII or factor IX, there is accelerated clearance of and suboptimal or absent rise in measured activity of infused factor, and the aPTT does not correct on mixing. The Bethesda assay measures the potency of the inhibitor.

Treatment

A. Factor VIII or IX Products

Plasma-derived or recombinant factor VIII or IX products are the mainstay of treatment. The optimal care for individuals with severe hemophilia is primary prophylaxis: by the age of 4 years, most children with severe hemophilia have begun twice- or thrice-weekly infusions of factor to prevent the recurrent joint bleeding that otherwise would characterize the disorder and lead to severe musculoskeletal morbidity. In selected cases of less severe hemophilia, or as an adjunct to prophylaxis in severe hemophilia, treatment with factor products is given peri-procedurally, prior to high-risk activities (such as sports), or as needed for bleeding episodes (Table 14–8). Recombinant factor VIII and factor IX molecules that are bioengineered to have an extended half-life may allow for extended dosing intervals in patients who are treated prophylactically. The decision to switch to a long-acting product is patient specific. The long-acting factor IX products have clear added value in reducing frequency of factor injections often to weekly or less. Long-acting factor VIII products have not achieved a similar degree of extended half-life. Patients with mild hemophilia A may respond to as-needed (on demand) intravenous or intranasal DDAVP. Antifibrinolytic agents may be useful in cases of mucosal bleeding and are commonly used adjunctively, such as following dental procedures.

B. Factor VIII or IX Inhibitors

Factor inhibitors (antibodies that interfere with activity or half-life) are a major clinical problem for patients with hemophilia. It may be possible to overcome low-titer inhibitors (less than 5 Bethesda units [BU]) by giving larger doses of factor, whereas treatment of bleeding in the presence of a high-titer inhibitor (more than 5 BU) requires infusion of an activated prothrombin complex concentrate (such as FEIBA [factor eight inhibitor bypassing activity]) or recombinant activated factor VII. Recombinant porcine factor VIII is also an option but is reserved for selective circumstances because of its cost. Inhibitor tolerance induction, achieved by giving large doses (50–300 units/kg intravenously of factor VIII daily) for 6–18 months, succeeds in eradicating the inhibitor in 70% of patients with hemophilia A and in 30% of patients with hemophilia B. Patients with hemophilia B who receive inhibitor tolerance induction, however, are at risk for development of nephrotic syndrome and anaphylactic reactions, making eradication of their inhibitors more problematic. Additional immunomodulation may allow for eradication in selected inhibitor tolerance induction–refractory patients. Emicizumab is a novel bi-specific antibody that brings activated factor IX and factor X together, effectively replacing the cofactor function of factor VIII in the clotting cascade, providing a major therapeutic advance for patients with inhibitors. Emicizumab has also been demonstrated to be an effective option for patients without inhibitors. It is given subcutaneously weekly, every other week, or every 4 weeks, making it easier to administer than intravenous factor products.

C. Gene Therapy

Gene therapy clinical trials for hemophilia A and B have shown great promise for patients with severe hemophilia A

Table 14–8. Treatment of bleeding in selected inherited disorders of hemostasis.

Disorder	Subtype	Treatment for Minor Bleeding	Treatment for Major Bleeding	Comment
Hemophilia A	Mild Moderate or severe	DDAVP[1] Factor VIII product	DDAVP[1] or factor VIII product Factor VIII product	Treat for 3–10 days for major bleeding or following surgery, keeping factor activity level 50–80% initially. Adjunctive EACA may be useful for mucosal bleeding or procedures
Hemophilia B	Mild, moderate, or severe	Factor IX product	Factor IX product	
von Willebrand disease	Type 1 Type 2 Type 3	DDAVP[1] DDAVP,[1] vWF product vWF product	DDAVP,[1] vWF product vWF product vWF product	
Factor XI deficiency	—	FFP or EACA	FFP	Adjunctive EACA should be used for mucosal bleeding or procedures

[1]Mild hemophilia A and type 2A or 2B vWD patients: therapeutic trial must have previously confirmed an adequate response (ie, elevation of factor VIII or vWF activity level into the normal range) and (for type 2B) no exacerbation of thrombocytopenia. DDAVP is not typically effective for type 2M vWD. A vWF-containing factor VIII concentrate is preferred for treatment of type 2N vWD.

Notes:

DDAVP dose is 0.3 mcg/kg intravenously in 50 mL saline over 20 minutes, or nasal spray 300 mcg for weight > 50 kg or 150 mcg for < 50 kg, every 24 hours, maximum of three doses in a 72-hour period. If more than two doses are used in a 48-hour period, free water restriction and monitoring for hyponatremia is essential.

EACA dose is 50 mg/kg orally four times daily for 3–5 days; maximum 24 g/day, useful for mucosal bleeding/dental procedures.

Factor VIII product dose is 50 units/kg for severe hemophilia A intravenously initially followed by 25 units/kg every 8 hours followed by lesser doses at longer intervals once hemostasis has been established.

Factor IX product dose is 100 units/kg (120 units/kg if using Benefix) intravenously initially for severe hemophilia B followed by 50 units/kg (60 units/kg if using Benefix) every 8 hours followed by lesser doses at longer intervals once hemostasis has been established.

vWF-containing factor VIII product dose is 60–80 RCoF units/kg intravenously every 12 hours initially followed by lesser doses at longer intervals once hemostasis has been established.

FFP is typically administered in 4-unit boluses and may not need to be re-bolused after the initial administration due to the long half-life of factor XI.

DDAVP, desmopressin acetate; EACA, epsilon-aminocaproic acid; FFP, fresh frozen plasma; vWF, von Willebrand factor.

and B. For most patients, gene therapy has eliminated spontaneous bleeding as well as the need for factor replacement. While phase 3 clinical trials have been restricted to patients 18 years of age and older, the results look extremely promising. It is hoped that this potentially life-changing therapy will become an approved treatment outside of clinical trials in late 2022.

D. Antiretroviral Therapy

Antiretroviral treatment should be administered to hemophilia patients with HIV infection. Patients with hepatitis C infection should be referred for treatment to eradicate the virus.

When to Refer

All patients with hemophilia should be seen regularly in a comprehensive hemophilia treatment center.

When to Admit

- Major invasive procedures because of the need for serial infusions of clotting factor concentrate.
- Bleeding that is unresponsive to outpatient treatment.

George LA et al. Hemophilia B gene therapy with a high-specific-activity factor IX variant. N Engl J Med. 2017; 377:2215. [PMID: 29211678]

Mahlangu J et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med. 2018;379:811. [PMID: 30157389]

Manco-Johnson MJ et al; Joint Outcomes Committee of the Universal Data Collection, US Hemophilia Treatment Center Network. Prophylaxis usage, bleeding rates, and joint outcomes of hemophilia, 1999 to 2010: a surveillance project. Blood. 2017;129:2368. [PMID: 28183693]

Oldenburg J et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med. 2017;377:809. [PMID: 28691557]

Pasi KJ et al. Multiyear follow-up of AAV5-hFVIII-SQ gene therapy for hemophilia A. N Engl J Med. 2020;382:29. [PMID: 31893514]

2. von Willebrand Disease

ESSENTIALS OF DIAGNOSIS

- The most common inherited bleeding disorder.
- vWF binds platelets to subendothelial surfaces, aggregates platelets, and prolongs the half-life of factor VIII.

General Considerations

vWF is an unusually large multimeric glycoprotein that binds to subendothelial collagen and its platelet receptor, glycoprotein Ib, bridging platelets to the subendothelial matrix at the site of vascular injury and contributing to linking them together in the platelet plug. vWF also has a binding site for factor VIII, prolonging factor VIII half-life in the circulation.

Between 75% and 80% of patients with vWD have type 1, a *quantitative abnormality* of the vWF molecule that usually does not feature an identifiable causal mutation in the vWF gene.

Type 2 vWD is seen in 15–20% of patients with vWD. In type 2A or 2B vWD, a *qualitative defect* in the vWF molecule is causative. Types 2N and 2M vWD are due to defects in vWF that decrease binding to factor VIII or to platelets, respectively. Type 2M vWD features a normal multimer pattern. Importantly, type 2N vWD can clinically resemble hemophilia A because factor VIII activity levels are decreased, and vWF activity and antigen (Ag) are normal. Type 3 vWD is rare, and like type 1, is a quantitative defect, with mutational homozygosity or compound heterozygosity yielding very low levels of vWF and severe bleeding in infancy or childhood. Due to its factor VIII carrier function, a severely low vWF level leads to low factor VIII activity and prolonged aPTT.

Clinical Findings

A. Symptoms and Signs

Patients with type 1 vWD usually have mild or moderate platelet-type bleeding (mucocutaneous) that may be evident in childhood. Heavier bleeding may occur with menses, surgery, or following delivery. Patients with type 2 vWD usually have moderate to severe bleeding that presents in childhood or adolescence. Patient with type 3 vWD demonstrate a severe bleeding phenotype that typically manifests in childhood or infancy.

B. Laboratory Findings

In type 1 vWD, the vWF activity (ristocetin co-factor or VWF:GPIbM assay) and the vWF Ag are mildly depressed, whereas the vWF multimer pattern is normal (Table 14–9). Laboratory testing of type 2A or 2B vWD typically shows a ratio of vWF Ag:vWF activity of approximately 2:1 and a multimer pattern that lacks the highest molecular weight multimers. Thrombocytopenia is common in type 2B vWD due to a gain-of-function mutation of the vWF molecule, which leads to increased vWF binding to its receptor on platelets, resulting in platelet clearance; a ristocetin-induced platelet aggregation (RIPA) study shows an increase in platelet aggregation in response to low concentrations of ristocetin. Except in the more severe forms of vWD that feature a significantly decreased factor VIII activity, aPTT is most commonly normal in patients with vWD. The PT is not affected by vWD. vWD type 2N has normal vWF antigen and activity but a low factor VIII due to impaired vWF binding to factor VIII.

Treatment

The treatment of vWD is outlined in Table 14–8. DDAVP is useful in the treatment of mild bleeding in most cases of type 1 and some cases of type 2 vWD. DDAVP causes release of vWF and factor VIII from storage sites (endothelial cells), leading to a two- to sevenfold increase in vWF and factor VIII. A therapeutic DDAVP trial to document sufficient rise in vWF level is critical prior to relying on DDAVP as a treatment option. Due to tachyphylaxis and the risk of significant hyponatremia secondary to fluid retention, DDAVP treatment should be limited to one dose per 24 hours and no more than three doses over 5 days. vWF-containing factor VIII concentrates or recombinant VWF products are used in all other clinical scenarios, and when bleeding is not controlled with DDAVP. Cryoprecipitate is no longer used as a source of vWD in clinical practice. Antifibrinolytic agents (eg, aminocaproic acid or tranexamic acid) may be used adjunctively for mucosal bleeding or procedures. Pregnant patients with type 1 vWD usually do not require treatment at the time of delivery because of the physiologic increase in vWF levels (up to threefold that of baseline) that are observed by parturition. However, levels need to be confirmed in late pregnancy, and if they are low or if excessive bleeding is encountered, vWF products may be given. Moreover, patients are at risk for significant bleeding 1–2 weeks postpartum when vWF levels fall secondary to the fall in estrogen levels and related return to baseline vWF levels.

James PD et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. Blood Adv. 2021;5:280. [PMID: 33570651]

Table 14–9. Laboratory diagnosis of von Willebrand disease.

Type		vWF Activity	vWF Antigen	Factor VIII	RIPA	Multimer Pattern
1		↓	↓	Nl or ↓	↓	Normal pattern; uniform ↓ intensity of bands
2	A	↓↓	↓	↓	↓	Large and intermediate multimers decreased or absent
	B	↓↓	↓	↓	↑	Large multimers decreased or absent
	M	↓	↓	↓	↓	Normal pattern; uniform ↓ intensity of bands
	N	Nl	Nl	↓↓	Nl	Nl
3		↓↓↓	↓↓↓	↓↓↓	↓↓↓	Multimers absent

Nl, normal; RIPA, ristocetin-induced platelet aggregation; vWF, von Willebrand factor.

3. Factor XI Deficiency

Factor XI deficiency (also called hemophilia C) is inherited in an autosomal recessive manner, leading to heterozygous, compound heterozygous, or homozygous defects. It is most prevalent among individuals of Ashkenazi Jewish descent but is in the differential diagnosis of any unexplained prolonged aPTT. In contrast to hemophilia A and B, factor XI levels do not correlate well with bleeding symptoms. Mild bleeding is most common, and diagnosis is often made after unexpected, excessive bleeding following surgery or trauma. Importantly, factor XI deficiency that can lead to provoked excessive bleeding does not always prolong the aPTT. FFP is the mainstay of treatment when plasma-derived factor XI concentrate is not available. Adjunctive aminocaproic acid or tranexamic acid is administered for procedures or bleeding episodes involving the mucosa (Table 14–8).

Verghese L et al. Management of parturients with factor XI deficiency—10 year case series and review of literature. Eur J Obstet Gynecol Reprod Biol. 2017;215:85. [PMID: 28622635]

4. Less Common Heritable Disorders of Coagulation

Congenital deficiencies of clotting factors II, V, VII, and X are rare and typically are inherited in an autosomal recessive pattern. A prolongation in the PT (and aPTT for factor X, factor V, and factor II deficiency) that corrects upon mixing with normal plasma is typical. Definitive diagnosis requires testing for specific factor activity. The treatment of factor II deficiency is with a prothrombin complex concentrate; factor V deficiency is treated with infusions of FFP or platelets (which contain factor V in alpha granules); factor VII deficiency is treated with recombinant human activated factor VII. Factor X deficiency is treated with an FDA-approved plasma-derived factor X product (Coagadex).

Deficiency of factor XIII characteristically leads to delayed bleeding that occurs hours to days after a hemostatic challenge, such as surgery or trauma. The condition is usually life-long, and spontaneous intracranial hemorrhages as well as recurrent pregnancy loss appear to occur with increased frequency in these patients compared with other congenital deficiencies. Cryoprecipitate can be used to provide factor XIII, but if available, plasma-derived factor XIII concentrate (Corifact) is preferred to treat bleeding or for surgical prophylaxis. Regular prophylactic factor XIII replacement is indicated for patients with severe factor XIII deficiency. Factor XIII has an A and B subunit. Recombinant factor XIII A-subunit (Tretten) is an option for patients deficient in the factor XIII A subunit. Factor XIII deficiency does not cause a prolongation of the PT or aPTT.

National Hemophilia Foundation. Products Licensed in the US. https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/products-licensed-in-the-us8

Peyvandi F et al. Treatment of rare factor deficiencies in 2016. Hematology Am Soc Hematol Educ Program. 2016;2016:663. [PMID: 27913544]

ACQUIRED DISORDERS OF COAGULATION

1. Acquired Antibodies to Factor II

Patients with antiphospholipid antibodies occasionally have antibody specificity to coagulation factor II (prothrombin) that accelerates factor II clearances and can lead to severe hypoprothrombinemia and bleeding. Mixing studies may or may not reveal the presence of an inhibitor, as the antibody typically binds to a non-enzymatically active portion of the molecule leading to accelerated clearance, but characteristically the PT is prolonged and levels of factor II are low. FFP should be administered to treat bleeding. Treatment is immunosuppressive.

2. Acquired Antibodies to Factor V

Products containing bovine factor V (such as topical thrombin or fibrin glue, frequently used in surgical procedures) can lead to formation of an anti–factor V antibody that cross-reacts with human factor V. Clinicopathologic manifestations range from a prolonged PT in an otherwise asymptomatic individual to severe bleeding. Mixing studies suggest the presence of an inhibitor, and the factor V activity level is low. In cases of serious or life-threatening bleeding, IVIG or platelet transfusions, or both, should be administered, and immunosuppression (as for acquired inhibitors to factor VIII) may be offered.

3. Acquired Antibodies to Factor VIII

Acquired hemophilia A due to factor VIII inhibitors is the most common acquired factor-specific bleeding disorder. Spontaneous antibodies to factor VIII can occur in adults without a prior history of hemophilia; older adults and patients with lymphoproliferative malignancy or autoimmune disease and those who are postpartum or postsurgical are at highest risk. The clinical presentation, which should be viewed as a medical emergency, typically includes extensive soft tissue ecchymoses, hematomas, and mucosal bleeding, as opposed to hemarthrosis characteristic of congenital hemophilia A. The aPTT is typically prolonged and does not correct upon mixing; factor VIII activity is low and a Bethesda assay reveals the titer of the inhibitor. Inhibitors of low titer (less than 5 BU) may often be overcome by infusion of high doses of factor VIII concentrates, whereas high-titer inhibitors (greater than 5 BU) must be treated with serial infusions of activated prothrombin complex concentrates, recombinant human activated factor VII, or recombinant porcine factor VIII. Emicizumab is also a treatment option. Along with establishment of hemostasis by one of these measures, immunosuppressive treatment with corticosteroids with or without oral cyclophosphamide or rituximab must be instituted to eradicate the autoantibody. Treatment with IVIG and plasmapheresis can be considered in refractory cases. Unlike in congenital factor VIII deficiency of hemophilia A, the patient's bleeding does not correlate well with the factor VIII activity level, so the clinician must be concerned with any elevation of aPTT secondary to acquired factor VIII inhibitor. All such patients require immediate referral to a hematologist.

Gibson CJ et al. Clinical problem-solving. A bruising loss. N Engl J Med. 2016;375:76. [PMID: 27406351]
Thomas VM et al. Off-label use of emicizumab in persons with acquired haemophilia A and von Willebrand disease: a scoping review of the literature. Haemophilia. 2022;28:4. [PMID: 34820989]

4. Vitamin K Deficiency

Vitamin K deficiency may occur as a result of deficient dietary intake of vitamin K (from green leafy vegetables, soybeans, and other sources), malabsorption, or decreased production by intestinal bacteria (due to treatment with chemotherapy or antibiotics). Vitamin K is required for normal function of vitamin K epoxide reductase that assists in posttranslational gamma-carboxylation of the coagulation factors II, VII, IX, and X, which is necessary for their activity. Thus, mild to moderate vitamin K deficiency typically features a prolonged PT (activity of the vitamin K–dependent factors is more reflected than in the aPTT; aPTT is prolonged if the deficiency is more severe) that corrects upon mixing; activity levels of individual clotting factors II, VII, IX, and X typically are low. Importantly, a concomitantly low factor V activity level is not indicative of isolated vitamin K deficiency and may indicate an underlying defect in liver synthetic function. Hospitalized patients on broad-spectrum antibiotics and with poor or no oral intake are at high risk for vitamin K deficiency.

For treatment, vitamin K_1 (phytonadione) may be administered via intravenous or oral routes; the subcutaneous route is not recommended due to erratic absorption. The oral dose is 5–10 mg/day and absorption is typically excellent; at least partial improvement in the PT should be observed within 18–24 hours of administration. Intravenous administration results in faster normalization of a prolonged PT than oral administration; due to infrequent reported serious adverse reactions, parenteral doses should be administered slowly (eg, over 30 minutes) with concomitant monitoring.

5. Coagulopathy of Liver Disease

Impaired liver function due to cirrhosis or other causes leads to decreased synthesis of clotting factors, including factors II, V, VII, IX, X, and fibrinogen; factor VIII levels, largely made in endothelial cells, may be elevated despite depressed levels of other coagulation factors. The PT (and with advanced disease, the aPTT) is typically prolonged and usually corrects on mixing with normal plasma. A normal factor V level, with decreased activity of factors II, VII, IX, and X suggests vitamin K deficiency rather than liver disease. Qualitative and quantitative deficiencies of fibrinogen also are prevalent among patients with advanced liver disease, typically leading to a prolonged PT, thrombin time, and reptilase time.

The coagulopathy of liver disease usually does not require hemostatic treatment unless bleeding occurs. Infusion of FFP may be considered if active bleeding is present and the aPTT and PT are prolonged; however, the effect is transient and concern for volume overload may limit infusions. Patients with bleeding and a fibrinogen level consistently below 80–100 mg/dL should receive cryoprecipitate. Liver transplantation, if feasible, results in production of coagulation factors at normal levels. The use of recombinant human activated factor VII in patients with bleeding varices is controversial, although some patient subgroups may experience benefit. The coagulopathy of liver disease can predispose to bleeding or thrombosis, so caution and experience are needed for optimal management.

Hunt BJ. Bleeding and coagulopathies in critical care. N Engl J Med. 2014;370:847. [PMID: 24571757]
Saner FH et al. Assessment and management of coagulopathy in critically-ill patients with liver failure. Curr Opin Crit Care. 2019;25:179. [PMID: 30855324]
Tripodi A et al. Changing concepts of cirrhotic coagulopathy. Am J Gastroenterol. 2017;112:274. [PMID: 27801884]

6. Warfarin Ingestion

See Antithrombotic Therapy section, below.

7. Disseminated Intravascular Coagulation

See above.

8. Heparin/Fondaparinux/Direct-Acting Oral Anticoagulant Use

See Classes of Anticoagulants, below.

9. Lupus Anticoagulants

Lupus anticoagulants prolong the aPTT by interfering with interactions between the clotting cascade and the phospholipid surface on which they function, but they do not lead to bleeding. Rather, they predispose to thrombosis. Lupus anticoagulants were so named because of their early identification in patients with autoimmune disease, although they also occur with increased frequency in individuals with underlying infection, inflammation, or malignancy, and they also can occur in asymptomatic individuals in the general population. A prolongation in the aPTT is observed that does not correct completely on mixing but that normalizes with excessive phospholipid. Specialized testing such as a positive hexagonal phase phospholipid neutralization assay, a prolonged dilute Russell viper venom time, and positive platelet neutralization assays can confirm the presence of a lupus anticoagulant. Rarely, the antibodies also interfere with factor II activity, and that tiny subset of lupus anticoagulant patients are at risk for bleeding.

Müller-Calleja N et al. Tissue factor pathway inhibitor primes monocytes for antiphospholipid antibody-induced thrombosis. Blood. 2019;134:1119. [PMID: 31434703]

OTHER CAUSES OF BLEEDING

Occasionally, abnormalities of the vasculature and integument may lead to bleeding despite normal hemostasis; congenital or acquired disorders may be causative. Congenital abnormalities include Ehlers-Danlos syndrome, osteogenesis imperfecta, hereditary hemorrhagic

telangiectasia (Osler-Weber-Rendu disease) (see Chapter 40), and Marfan syndrome. Acquired disorders include integument thinning due to prolonged corticosteroid administration or normal aging, amyloidosis, vasculitis, and scurvy (acquired defects). The bleeding time often is prolonged. If possible, treatment of the underlying condition should be pursued, but if this is not possible or feasible (ie, congenital syndromes), globally hemostatic agents such as antifibrinolytic agents or DDAVP can be considered for treatment of bleeding.

ANTITHROMBOTIC THERAPY

The currently available anticoagulants include unfractionated heparin, LMWHs, fondaparinux, vitamin K antagonists (ie, warfarin), and DOACs (ie, dabigatran, rivaroxaban, apixaban, edoxaban). (For a discussion of injectable DTIs, see section Heparin-Induced Thrombocytopenia above.)

Classes of Anticoagulants

A. Unfractionated Heparin and LMWHs

About one-third of the molecules in a given preparation of unfractionated heparin contain the crucial pentasaccharide sequence necessary for binding of antithrombin and exerting its anticoagulant effect upon thrombin. The degree of anticoagulation with unfractionated heparin is typically monitored by aPTT or anti-Xa level in patients who are receiving the drug in therapeutic doses, although the pharmacokinetics of unfractionated heparin are poorly predictable. Only a fraction of an infused dose of heparin is metabolized by the kidneys, making it safe to use in most patients with significant kidney disease.

Due to less protein and cellular binding, pharmacokinetics of the LMWHs are much more predictable than those of unfractionated heparin, allowing for fixed weight-based dosing. All LMWHs are principally renally cleared and must be avoided or used with extreme caution in individuals with creatinine clearance less than 30 mL/minute. Compared to unfractionated heparin, LMWHs have a longer half-life, which allows once- or twice-daily subcutaneous dosing and thus greater convenience and outpatient therapy in selected cases. Most patients do not require monitoring, although monitoring using the anti-Xa activity level is appropriate for patients with moderate kidney disease, those with elevated BMI or low weight, and selected pregnant patients. LMWHs are associated with a lower frequency of HIT and thrombosis (approximately 0.6%) than unfractionated heparin (3%).

B. Fondaparinux

Fondaparinux is a synthetic molecule consisting of the highly active pentasaccharide sequence found in LMWHs. As such, it exerts almost no thrombin inhibition and works to indirectly inhibit factor Xa through binding to antithrombin. Fondaparinux, like the LMWHs, is almost exclusively metabolized by the kidneys, and should be avoided in patients with creatinine clearance less than 30 mL/minute. Predictable pharmacokinetics allow for weight-based dosing.

C. Vitamin K Antagonist (Warfarin)

The vitamin K antagonist warfarin inhibits the activity of the vitamin K–dependent carboxylase that is important for the posttranslational modification of coagulation factors II, VII, IX, and X. Although warfarin is taken orally, which is a significant advantage over the heparins and heparin derivatives, interindividual differences in nutritional status, comorbid diseases, concomitant medications, and genetic polymorphisms lead to a poorly predictable anticoagulant response. Individuals taking warfarin must undergo periodic monitoring to verify the intensity of the anticoagulant effect, reported as the INR, which corrects for differences in potency of commercially available thromboplastin used to perform the PT.[1]

D. Direct-Acting Oral Anticoagulants

Unlike warfarin, the DOACs act directly against coagulation factors. Dabigatran is a DTI; rivaroxaban, apixaban, and edoxaban are direct factor Xa inhibitors. DOACs (1) have a predictable dose effect and therefore do not require laboratory monitoring, (2) have anticoagulant activity independent of vitamin K with no need for dietary stasis, and (3) are renally metabolized to varying degrees so there are restrictions or dose reductions related to reduced kidney function (Table 14–10). While the DOACs have fewer drug interactions than warfarin, if DOACs are given with potentially interacting medications, there is no reliable way to measure the impact on anticoagulant activity of the concomitant administration. There is also no reliable way to measure adherence. The clinician must carefully consider kidney function, concomitant medications, indication for use, candidacy for lead-in parenteral therapy (as required for acute VTE treatment with edoxaban and dabigatran only) and anticipated patient adherence. Providers must be careful to dose each DOAC properly for the indication, kidney function, and weight of patient, and to check for drug interactions. (See Table 14–10 for details.) For morbidly obese patients (more than 120 kg or BMI $\geq$ 40), standard doses of apixaban or rivaroxaban should be chosen rather than dabigatran or edoxaban. DOACs are not recommended for VTE treatment in the acute setting following bariatric surgery due to concerns regarding absorption but can be considered for ongoing treatment after the initial 4 weeks of therapy; when available, apixaban or rivaroxaban trough levels can be checked to ensure they are within expected ranges. Reversal agents are available for the oral DTI (dabigatran) and for the factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) (Table 14–11).

Routine monitoring is not recommended for patients taking DOACs. However, there are clinical scenarios where assessing anticoagulant activity may be helpful, including active bleeding, pending urgent surgery, suspected therapeutic failure, or concern for accumulation. Drug-specific anti-Xa levels are not widely available, and guidance is

[1]Importantly, because the INR is not standardized for abnormalities of factor V and fibrinogen, the INR should be used only in reference to anticoagulation in patients who are receiving warfarin.

Table 14–10. DOACs for VTE treatment and prevention.[1] Dosing for atrial fibrillation is provided in Table 10–13.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Approved uses for VTE	VTE treatment and secondary prevention VTE prophylaxis post-hip replacement	VTE treatment and secondary prevention VTE prophylaxis post-hip or knee replacement VTE prophylaxis in select adult patients hospitalized for acute medical illness	VTE treatment and secondary prevention VTE prophylaxis post-hip or knee replacement	VTE treatment and secondary prevention
Frequency of dosing for VTE	Twice daily following 5-day parenteral lead-in for acute VTE	Twice daily for first 21 days of acute VTE therapy, then daily Once daily for DVT prophylaxis	Twice daily	Once daily following 5-day parenteral lead-in for acute VTE
Food	With or without food	With food (for 15- and 20-mg tablets)	With or without food	With or without food
Crushable?	No	Can crush; do not administer via J tube	Can crush and administer orally or via NG tube	No data
Renal clearance	80%	30–60%	25%	50%
Kinetics	t ½ = 12–17 hours; tmax = 2 hours	t ½ = 5–9 hours; tmax = 3 hours	t ½ = 12 hours; tmax = 3 hours	t ½ = 10–14 hours; tmax = 2 hours
Impact on INR	↑ (or →)	↑↑ (or → at low concentrations)	↑ (or →)	↑
Impact on aPTT	↑↑	↑	↑	↑
Drug interactions (list not comprehensive)	**Avoid** rifampin, St John's wort, and possibly carbamazepine **Caution** with amiodarone, clarithromycin, dronedarone, ketoconazole, quinidine, verapamil No dose adjustment if CrCl > 50 mL/minute **Reduce dose** to 75 mg orally twice daily if CrCl 30–50 mL/minute and concurrent use of dronedarone or ketoconazole	**Avoid** carbamazepine, conivaptan, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, phenytoin, rifampin, ritonavir, St John's wort **Caution** with the concurrent use of combined P-gp inhibitors and/or weak or moderate inhibitors of CYP3A4 (eg, amiodarone, azithromycin, diltiazem, dronedarone, erythromycin, felodipine, quinidine, ranolazine, verapamil) particularly in patients with impaired kidney function	**Avoid** carbamazepine, phenytoin, rifampin, St John's wort. If on apixaban 5 mg twice daily, decrease to 2.5 mg twice daily if starting itraconazole, ketoconazole, or ritonavir. If already on decreased dose of apixaban, avoid co-administration. **Caution** with clarithromycin	**Avoid** rifampin **Reduce dose** with certain P-gp inhibitors (eg, amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin). Use has not been studied with many other P-gp inhibitors and inducers. Some experts recommend avoiding concurrent use altogether
Switching from DOAC to warfarin (per AC Forum Clinical Guidance)	Start warfarin and overlap with dabigatran; CrCl C50 mL/minute, overlap 3 days CrCl 30–50 mL/minute, overlap 2 days CrCl 15–30 mL/minute, overlap 1 day	Stop DOAC; start warfarin and LMWH at time of next scheduled DOAC dose and bridge until INR ≥ 2.0	Stop DOAC; start warfarin and LMWH at time of next scheduled DOAC dose and bridge until INR ≥ 2.0	For 60-mg dose, reduce dose to 30 mg and start warfarin concomitantly For 30-mg dose, reduce dose to 15 mg and start warfarin concomitantly Stop edoxaban when INR ≥ 2.0
Warfarin to DOAC	Start when INR < 2.0	Start when INR < 3.0	Start when INR < 2.0	Start when INR ≤ 2.5
Special considerations	Dyspepsia is common and starts within first 10 days GI bleeding risk higher with dabigatran than with warfarin	GI bleeding risk higher with rivaroxaban than with warfarin		Do not use if CrCl < 15 mL/minute

Table 14–11. Medications to consider for reversing anticoagulant effect during life-threatening bleeding.[1]

Anticoagulants	Guidance
Parenteral	
Heparins	Protamine provides total (for unfractionated heparin) or partial (for LMWHs) reversal of anticoagulant effect. • Administration: Very slow infusion • Maximum dose: 50 mg intravenously • Caution: risk of anaphylactoid reactions and true hypersensitivity reactions, especially if allergy to other protamine-containing medications (such as NPH insulin) or to fish (black box warning) • Dosing depends on dose given and time elapsed • Dosing calculator at https://clincalc.com/Protamine/
Unfractionated heparin	Protamine (100% neutralization) • 1 mg protamine neutralizes approximately 100 units of heparin sulfate • Monitor drug activity with aPTT and/or heparin anti-Xa activity
LMWH (enoxaparin, dalteparin)	Protamine (approximately 60% neutralization) • Last dose < 8 hours ago: 1 mg protamine for each 100 units of dalteparin or 1 mg enoxaparin • Last dose > 8 hours ago: 0.5 mg protamine for each 100 units of dalteparin or 1 mg enoxaparin • Degree of reversal can be assessed with LMWH anti-Xa activity
Oral	
DOACs	Guidance for all DOAC-associated major bleeding: • Supportive measures recommended for all patients • If ingested within 2 hours, administer activated charcoal • Reversal agent is recommended ONLY if bleeding is life-threatening or into a critical organ • Reversal agent is not recommended for DOAC overdose without bleeding
Dabigatran	Idarucizamab 5 g intravenously once If idarucizamab is not available: administer APCC 50 units/kg intravenously
Apixaban	Andexanet alfa: Last dose ≤ 5 mg AND within 8 hours: low dose[2] Last dose > 5 mg AND within 8 hours: high dose[3] Last dose > 8 hours ago: low dose[2] If andexanet alfa is not available: administer four-factor PCC 2000 units
Rivaroxaban	Andexanet alfa: Last dose ≤ 10 mg AND within 8 hours: low dose[2] Last dose > 10 mg AND within 8 hours: high dose[3] Last dose > 8 hours ago: low dose[2] If andexanet alfa is not available: administer four-factor PCC 2000 units
Warfarin	See Table 14–21

[1]Guidance adopted from 2019 Anticoagulation Forum and American Society of Hematology 2019 guidelines.
[2]Low-dose andexanet alfa: initial 400 mg intravenous bolus at target rate of 30 mg/minute followed by continuous infusion at 4 mg/minute for up to 120 minutes.
[3]High-dose andexanet alfa: initial 800 mg intravenous bolus at target rate of 30 mg/minute followed by continuous infusion at 8 mg/minute for up to 120 minutes. Begin infusion within 2 minutes after intravenous bolus to prevent rebound anti-Xa activity.
APCC, three-factor prothrombin complex concentrate; FFP, fresh frozen plasma; LMWH, low-molecular-weight heparin; PCC, four-factor prothrombin complex concentrate.
Data from Cuker A et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. Am J Hematol. 2019;94(6):697–709; data from Witt DM et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018;2(22):3257–3291.

lacking regarding clinical approach to the results. DOACs have varying effects on the PT and aPTT. In the absence of drug-specific levels, a normal dilute thrombin time excludes the presence of clinically relevant dabigatran levels; an elevated aPTT suggests clinically relevant levels of dabigatran. An elevated PT suggests clinically relevant levels of rivaroxaban. However, a normal aPTT or normal PT does not rule out clinically significant amounts of dabigatran or rivaroxaban, respectively.

Douxfils J et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. J Thromb Haemost. 2018;16:209. [PMID: 29193737]

Prevention of Venous Thromboembolic Disease

The frequency of venous thromboembolic disease (VTE) among hospitalized patients ranges widely. Up to 60% of VTE cases occur during or after hospitalization, with

especially high incidence among critical care patients and high-risk surgical patients.

Avoidance of fatal PE, which occurs in up to 5% of high-risk inpatients as a consequence of hospitalization or surgery, is a major goal of pharmacologic prophylaxis. Tables 14–12 and 14–13 provide risk stratification for DVT/VTE among hospitalized surgical and medical inpatients. Standard pharmacologic prophylactic regimens are listed in Table 14–14; prophylactic anticoagulation regimens differ in their recommended duration of use. Prophylactic strategies should be guided by individual risk stratification, with all moderate- and high-risk patients receiving pharmacologic prophylaxis, unless contraindicated. Contraindications to VTE prophylaxis for hospital inpatients at high risk for VTE are listed in Table 14–15. In patients at high risk for VTE with absolute contraindications to pharmacologic prophylaxis, mechanical devices such as intermittent pneumatic compression devices should be used, ideally in portable form with at least an 18-hour daily wear time.

Table 14–12. Risk stratification for DVT/VTE among surgical inpatients.

High risk[1]
Recent major orthopedic surgery/arthroplasty/fracture
Abdominal/pelvic cancer undergoing surgery
Spinal cord injury[2] or major trauma within 90 days
More than three of the intermediate risk factors (see below)
Intermediate risk
Not ambulating independently outside of room at least twice daily
Active infectious or inflammatory process
Active malignancy
Major surgery (nonorthopedic)
History of VTE
Stroke
Central venous access or PICC line
IBD
Prior immobilization (> 72 hours) preoperatively
Obesity (BMI > 30)
Patient age > 50 years
Hormone replacement or oral contraceptive therapy
Hypercoagulable state
Nephrotic syndrome
Burns
Cellulitis
Varicose veins
Paresis
HF (systolic dysfunction)
COPD exacerbation
Low risk
Minor procedure and age < 40 years with no additional risk factors
Ambulatory with expected length of stay of < 24 hours or minor surgery

[1]Risk is highest in first month and persists for up to 90 days.
[2]Direct spinal cord trauma is a contraindication to VTE prophylaxis in the immediate post-injury period; consult with neurosurgical experts regarding timing of initiation.
HF, heart failure; PICC, peripherally inserted central catheter; VTE, venous thromboembolism.

Table 14–13. Padua Risk Assessment Model for VTE prophylaxis in hospitalized medical patients.

Condition	Points[1]
Active cancer, history of VTE, immobility, laboratory thrombophilia	3 points each
Recent (≤ 1 mo) trauma and/or surgery	2 points each
Age ≥ 70; acute MI or ischemic stroke; acute infection or rheumatologic disorder; BMI ≥ 30; hormonal therapy	1 point each

[1]A score ≥ 4 connotes high risk of VTE in the noncritically ill medical patients and pharmacologic prophylaxis is indicated, absent absolute contraindications.
CVA, cerebrovascular accident; VTE, venous thromboembolism.

1. Primary VTE prophylaxis for medical patients—It is recommended that VTE prophylaxis be used judiciously in hospitalized medical patients who are not critically ill since a comprehensive review of evidence suggested harm from bleeding in low-risk patients given low-dose heparin, and skin necrosis from compression stockings in stroke patients. Risk assessment models like the Padua Risk Score (Table 14–13) and the IMPROVE risk score can help clinicians identify patients who may benefit from DVT prophylaxis. The IMPROVE investigators also developed a bleeding risk model that may aid in identifying acutely ill medical inpatients at increased risk for bleeding: https://www.outcomes-umassmed.org/IMPROVE/risk_score/index.html. While two of the anti-Xa oral anticoagulants (rivaroxaban) have been approved for extended duration prophylaxis after discharge for medically ill patients, how to identify those who will have clinical benefit from this practice is still unclear. For the prevention of VTE in severe COVID-19, see below.

2. Primary VTE prophylaxis for surgical patients—The Caprini score may help guide decisions in surgical patients about VTE prophylaxis (https://www.mdcalc.com/caprini-score-venous-thromboembolism-2005). In addition, certain high-risk surgical patients should be considered for extended-duration prophylaxis of up to 1 month, including those undergoing total hip replacement, hip fracture repair, and abdominal and pelvic cancer surgery. If bleeding is present, if the risk of bleeding is high, or if the risk of VTE is high for the inpatient (Table 14–12) and therefore combined prophylactic strategies are needed, some measure of thromboprophylaxis may be provided through mechanical devices such as intermittent pneumatic compression devices and graduated compression stockings.

3. Primary VTE prophylaxis for ambulatory cancer patients—Some ambulatory cancer patients undergoing chemotherapy who are at moderate to high risk of VTE (Khorana risk score ≥ 2) (https://www.mdcalc.com/khorana-risk-score-venous-thromboembolism-cancer-patients) may benefit from pharmacologic DVT prophylaxis, although bleeding risk is increased and caution should be taken, particularly in patients with GI or intracranial malignancy, and other risk factors for

Table 14–14. Pharmacologic prophylaxis of VTE in selected clinical scenarios.[1]

Anticoagulant	Dose	Frequency	Clinical Scenario	Comment
LMWH and Fondaparinux				
Enoxaparin	40 mg subcutaneously	Once daily	Medical inpatients at high risk for VTE and most critical care patients[2]	—
			Surgical patients (moderate risk for VTE)	—
			Abdominal/pelvic cancer surgery	Consider continuing for 4 weeks total duration after abdominopelvic cancer surgery.
		Twice daily	Bariatric surgery	Higher doses may be required.
	30 mg subcutaneously	Twice daily	Orthopedic surgery[3]	Give for at least 10 days. For THR, TKR, or HFS, consider continuing up to 1 month after surgery in high-risk patients.
			Major trauma	Not applicable to patients with isolated lower extremity trauma.
			Spinal cord injury[4]	—
Dalteparin	2500 units subcutaneously	Once daily	Medical inpatients at high risk for VTE[2]	—
			Abdominal surgery (moderate risk for VTE)	Give for 5–10 days.
	5000 units subcutaneously	Once daily	Orthopedic surgery[3]	First dose = 2500 units. Give for at least 10 days. For THR, TKR, or HFS, consider continuing up to 1 month after surgery in high-risk patients.
			Abdominal surgery (higher risk for VTE)	Give for 5–10 days. Consider continuing for 4 weeks total duration after abdominopelvic cancer surgery.
			Medical inpatients	—
Fondaparinux	2.5 mg subcutaneously	Once daily	Orthopedic surgery[3]	Give for at least 10 days. For THR, TKR, or HFS, consider continuing up to 1 month after surgery in high-risk patients.
Direct-Acting Oral Anticoagulants				
Rivaroxaban	10 mg orally	Once daily	Orthopedic surgery: THR, TKR	Give for 12 days following TKR; give for 35 days following THR.
Apixaban	2.5 mg orally	Twice daily	Following THR or TKR	Give for 12 days following TKR; give for 35 days following THR.
Dabigatran	110 mg orally first day, then 220 mg	Once daily	Following THR	For patients with CrCl > 30 mL/minute. Consider continuing up to 1 month after surgery in high-risk patients.
Unfractionated Heparin				
Unfractionated heparin	5000 units subcutaneously	Three times daily	Higher VTE risk with low bleeding risk	Includes gynecologic surgery for malignancy and urologic surgery, medical patients with multiple risk factors for VTE.
	5000 units subcutaneously	Twice daily	Hospitalized patients at intermediate risk for VTE	Includes gynecologic surgery (moderate risk).
			Patients with epidural catheters	LMWHs usually avoided due to risk of spinal hematoma.
			Patients with severe kidney disease[5]	LMWHs contraindicated.

(*continued*)

Table 14–14. Pharmacologic prophylaxis of VTE in selected clinical scenarios.[1] (continued)

Anticoagulant	Dose	Frequency	Clinical Scenario	Comment
Warfarin and Aspirin				
Warfarin	(Variable) oral	Once daily	Orthopedic surgery[3]	Titrate to goal INR = 2.5. Give for at least 10 days. For high-risk patients undergoing THR, TKR, or HFS, consider continuing up to 1 month after surgery.
Aspirin	81 mg orally	Twice daily	TKR, THR	For patients at otherwise low VTE risk following major orthopedic surgery. Give for at least 14 days.

[1]All regimens administered subcutaneously, except for warfarin. See Table 14–15 for contraindications.
[2]See Prevention of Venous Thromboembolic Disease text, above, for definition of high-risk patients.
[3]Includes TKR, THR, and HFS.
[4]Direct spinal cord trauma is a contraindication to VTE prophylaxis in the immediate post-injury period; consult with neurosurgical experts regarding timing of initiation.
[5]Defined as creatinine clearance < 30 mL/minute.
CrCl, creatine clearance; HFS, hip fracture surgery; LMWH, low-molecular-weight heparin; P-gp, P-glycoprotein; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolic disease.

anticoagulant-related bleeding (such as thrombocytopenia and kidney dysfunction). DOACs should be avoided when there are possible interactions with chemotherapeutic agents.

Treatment of VTE Disease

A. Anticoagulant Therapy for VTE

Treatment for VTE should be offered to patients with objectively confirmed DVT or PE, or to those in whom the clinical suspicion is high for the disorder but who have not yet undergone diagnostic testing (see Chapter 9). The management of VTE primarily involves administration of anticoagulants; the goal is to prevent recurrence, extension and embolization of thrombosis and to reduce the risk of post-thrombotic syndrome. Suggested anticoagulation regimens are found in Table 14–16.

Table 14–15. Contraindications to VTE prophylaxis for medical or surgical hospital inpatients at high risk for VTE.

Absolute contraindications
Acute hemorrhage from wounds or drains or lesions
Intracranial hemorrhage within prior 24 hours
Heparin-induced thrombocytopenia (HIT): consider using fondaparinux
Severe trauma to head or spinal cord or extremities
Epidural anesthesia/spinal block within 12 hours of initiation of anticoagulation (concurrent use of an epidural catheter and anticoagulation other than low prophylactic doses of unfractionated heparin should require review and approval by service who performed the epidural or spinal procedure, eg, anesthesia/pain service, and in many cases, should be avoided entirely)
Currently receiving warfarin or heparin or LMWH or direct thrombin inhibitor for other indications
Relative contraindications
Coagulopathy (INR > 1.5)
Intracranial lesion or neoplasm
Severe thrombocytopenia (platelet count < 50,000/mcL [50 × 10^9/L])
Intracranial hemorrhage within past 6 months
GI or genitourinary hemorrhage within past 6 months

LMWH, low-molecular-weight heparin; VTE, venous thromboembolic disease.
Adapted from guidelines used at the Veterans Affairs Medical Center, San Francisco, CA.

B. Selecting Appropriate Initial Anticoagulant Therapy for VTE

Most patients with DVT alone may be treated as outpatients, provided that their risk of bleeding is low and they have good follow-up. Table 14–17 outlines proposed selection criteria for outpatient treatment of DVT.

Among patients with PE, risk stratification at time of diagnosis should direct treatment and triage. Patients with persistent hemodynamic instability are classified as high-risk patients (previously referred to as having "massive PE") and have an early PE-related mortality of more than 15%. These patients should be admitted to an ICU and generally receive thrombolysis and anticoagulation with intravenous heparin. Intermediate-risk patients (previously "submassive PE") have a mortality rate of up to 15% and should be admitted to a higher level of inpatient care, with consideration of thrombolysis on a case-by-case basis. Catheter-directed techniques, if available, may be an option for patients who are poor candidates for systemic thrombolysis and/or in centers with expertise. Low-risk patients have a mortality rate less than 3% and are candidates for expedited discharge or outpatient therapy.

For hemodynamically stable patients, additional assessment focusing on right ventricular dysfunction is warranted to differentiate between low-risk, low-intermediate risk, and high-intermediate risk PE. The Bova score (https://www.mdcalc.com/bova-score-pulmonary-embolism-complications) and the simplified PE severity index accurately identify patients at low risk for 30-day PE-related mortality (Table 14–18) who are potential candidates for expedited discharge or outpatient treatment.

Because the Bova score includes serum troponin and evidence of right ventricular dysfunction (by CT or echocardiography), it also identifies patients with high-intermediate risk PE who warrant close monitoring and may require escalation of therapy. An RV/LV ratio less than 1.0 on chest CT angiogram has been shown to have good negative predictive value for adverse outcome but suffers from inter observer variability. Echocardiography may provide better assessment of right ventricular dysfunction when there is concern. Serum biomarkers such as BNP and troponin are most useful for their negative predictive value, and mainly in combination with other predictors.

Selection of an initial anticoagulant should be determined by patient characteristics (kidney function, immediate bleeding risk, weight) and the clinical scenario (eg, whether thrombolysis is being considered, active cancer, thrombosis location) as described in Table 14–16.

1. Parenteral anticoagulants for VTE—

Heparins—In patients in whom parenteral anticoagulation is being considered, LMWHs are more effective than unfractionated heparin in the immediate treatment of DVT and PE; they are preferred as initial treatment because of predictable pharmacokinetics, which allow for subcutaneous, once- or twice-daily dosing with no requirement for monitoring in most patients. Accumulation of LMWH and increased rates of bleeding have been observed among patients with severe kidney disease (creatinine clearance less than 30 mL/minute), leading to a recommendation to use intravenous unfractionated heparin preferentially in these patients. *If concomitant thrombolysis is being considered, unfractionated heparin is preferred.* Patients with VTE and a perceived higher risk of bleeding (ie, post-surgery) may be better candidates for treatment with

Table 14–16. Initial anticoagulation for VTE.[1]

Anticoagulant	Dose/Frequency	Clinical Scenario					Comment
		DVT, Lower Extremity	DVT, Upper Extremity	PE	VTE, With Concomitant Severe Kidney Disease[2]	VTE, Cancer-Related	
Unfractionated Heparin							
Unfractionated heparin	80 units/kg intravenous bolus, then continuous intravenous infusion of 18 units/kg/hour	×	×	×	×		Bolus may be omitted if risk of bleeding is perceived to be elevated. Maximum bolus, 10,000 units. Requires aPTT or heparin anti-Xa monitoring. Most patients: begin warfarin at time of initiation of heparin.
	330 units/kg subcutaneously × 1, then 250 units/kg subcutaneously every 12 hours	×					Fixed-dose; no aPTT monitoring required
LMWH and Fondaparinux							
Enoxaparin[3]	1 mg/kg subcutaneously every 12 hours **or** 1.5 mg/kg subcutaneously daily	×	×	×			Most patients: begin warfarin at time of initiation of LMWH
Dalteparin[3]	200 units/kg subcutaneously once daily for first month, then 150 units/kg/day	×	×	×		×	Preferred LMWH for cancer patients; administer for at least 3–6 months (no transition to warfarin)
Fondaparinux	5–10 mg subcutaneously once daily; use 7.5 mg for body weight 50–100 kg; 10 mg for body weight > 100 kg	×	×	×			

(*continued*)

Table 14–16. Initial anticoagulation for VTE.[1] (continued)

Anticoagulant	Dose/Frequency	Clinical Scenario					Comment
		DVT, Lower Extremity	DVT, Upper Extremity	PE	VTE, With Concomitant Severe Kidney Disease[2]	VTE, Cancer-Related	
Direct-Acting Oral Anticoagulants (DOACs)							
Rivaroxaban	15 mg orally twice daily with food for 21 days, then 20 mg orally daily with food	×	×	×		×	Contraindicated if CrCl < 30 mL/minute Monotherapy without need for initial parenteral therapy Caution in luminal GI or genitourinary cancer
Apixaban	10 mg orally twice daily for first 7 days, then 5 mg twice daily	×	×	×		×	Contraindicated if CrCl < 25 mL/minute Monotherapy without need for initial parenteral therapy
Dabigatran	5–10 days of parenteral anticoagulation, then begin 150 mg orally twice daily	×	×	×			Contraindicated if CrCl < 15 mL/minute Initial need for parenteral therapy
Edoxaban	5–10 days of parenteral anticoagulation, then 60 mg orally once daily; 30 mg once daily recommended if CrCl is 15–50 mL/minute, if weight ≤ 60 kg, or if certain P-gp inhibitors are present	×	×	×		×	Contraindicated if CrCl < 15 mL/minute Initial need for parenteral therapy Caution in luminal GI or genitourinary cancer

[1]Obtain baseline hemoglobin, platelet count, aPTT, PT/INR, and creatinine prior to initiation of anticoagulation. *Anticoagulation is contraindicated in the setting of active bleeding.*
[2]Defined as creatinine clearance < 30 mL/minute.
[3]If body weight < 50 kg, reduce dose and monitor anti-Xa levels.
CrCl, creatinine clearance; P-gp, P-glycoprotein; VTE, venous thromboembolic disease (includes DVT and PE).
Note: An "×" denotes appropriate use of the anticoagulant.

unfractionated heparin than LMWH given its shorter half-life and reversibility. Unfractionated heparin can be effectively neutralized with protamine sulfate while protamine may only have partial reversal effect on LMWH. Use of unfractionated heparin leads to HIT and thrombosis in approximately 3% of patients, so daily CBCs are recommended during the initial 10–14 days of exposure.

Weight-based, fixed-dose daily subcutaneous fondaparinux may also be used for the initial treatment of DVT and PE, with no increase in bleeding over that observed with LMWH. Its lack of reversibility, long half-life, and renal clearance limit its use in patients with an increased risk of bleeding or kidney disease.

2. Oral anticoagulants for VTE—

A. Direct-acting oral anticoagulants— DOACs have a predictable dose effect, few drug-drug interactions, rapid onset of action, and freedom from laboratory monitoring (Table 14–10). Dabigatran, rivaroxaban, apixaban, and edoxaban are approved for treatment of acute DVT and PE. While rivaroxaban and apixaban can be used as monotherapy eliminating the need for parenteral therapy, patients treated with dabigatran or edoxaban must first receive 5–10 days of parenteral anticoagulation and then be transitioned to the oral agent per prescribing information. Unlike warfarin, DOACs do not require an overlap since these agents are immediately active; the DOAC is started when the parenteral agent is stopped. Compared to warfarin and LMWH, the DOACs are all noninferior with respect to prevention of recurrent VTE; both rivaroxaban and apixaban have a lower bleeding risk than warfarin with LMWH bridge. While DOACs are recommended as first-line therapy for acute VTE, agent selection should be individualized with consideration of kidney

Table 14–17. Patient selection for outpatient treatment of DVT.

Patients considered appropriate for outpatient treatment
No clinical signs or symptoms of PE and pain controlled
Confirmed ability to pay for medication (either by insurance or out-of-pocket)
Capable and willing to comply with frequent follow-up
Initially, patients may need to be seen daily to weekly
Potential contraindications for outpatient treatment
DVT involving inferior vena cava, iliac, common femoral, or upper extremity vein (these patients might benefit from vascular intervention)
Comorbid conditions requiring inpatient management
Active peptic ulcer disease, GI bleeding in past 14 days, liver synthetic dysfunction
Brain metastases, current or recent CNS or spinal cord injury/surgery in the last 10 days, CVA ≤ 4–6 weeks
Familial bleeding diathesis
Active bleeding from source other than GI
Thrombocytopenia
Creatinine clearance < 30 mL/minute
Weight < 55 kg (male) or < 45 kg (female)
Recent surgery, spinal or epidural anesthesia in the past 3 days
History of heparin-induced thrombocytopenia
Inability to reliably take medication at home, recognize changes in health status, or understand or follow directions

CVA, cerebrovascular accident.

function, concomitant medication use, indication, cost, and adherence. Heparins may be preferable as initial therapy when hospitalized patients have clinical instability and fluctuating renal or hepatic function; when bleeding risk is high; or when there is concern that thrombolysis may be required.

B. Warfarin—If warfarin is chosen as the oral anticoagulant it should be initiated along with the parenteral anticoagulant, which is continued until INR is in therapeutic range. Most patients require 5 mg of warfarin daily for initial treatment, but lower doses (2.5 mg daily) should be considered for patients of Asian descent, older adults, and those with hyperthyroidism, heart failure, liver disease, recent major surgery, malnutrition, certain polymorphisms for the *CYP2C9* or the *VKORC1* genes or who are receiving concurrent medications that increase sensitivity to warfarin. Conversely, individuals of African descent, those with larger BMI or hypothyroidism, and those who are receiving medications that increase warfarin metabolism (eg, rifampin) may require higher initial doses (7.5 mg daily). Daily INR results should guide dosing adjustments in the hospitalized patient while at least biweekly INR results guide dosing in the outpatient during the initial period of therapy (Table 14–19). Web-based warfarin dosing calculators incorporating clinical and genetic factors are available to help clinicians choose appropriate starting doses (eg, see www.warfarindosing.org). Because an average of 5 days is required to achieve a steady-state reduction in the activity of vitamin K–dependent coagulation factors, the parenteral anticoagulant should be continued for at least 5 days and until the INR is more than 2.0. Meticulous follow-up should be arranged for all patients taking warfarin because of the bleeding risk associated with initiation of therapy. Once stabilized, the INR should be checked at an interval no longer than every 6 weeks and warfarin dosing should be adjusted by guidelines (Table 14–20) since this strategy has been shown to improve the time patients spend in the therapeutic range and their clinical outcomes. Supratherapeutic INRs should be managed according to evidence-based guidelines (Table 14–21).

Table 14–18. Simplified Pulmonary Embolism Severity Index (PESI).

		Points
Age > 80 years old		1
Cancer		1
Chronic cardiopulmonary disease		1
Systolic blood pressure < 100 mm Hg		1
Oxygen saturation ≤ 90%		1
Severity Class	**Points**	**30-Day Mortality**
Low risk	0	1%
High risk	≥ 1	10%

Data from Jiménez D et al; RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170:1383.

C. Duration of Anticoagulation Therapy for VTE

The clinical scenario in which the thrombosis occurred is the strongest predictor of recurrence and, in most cases, guides duration of anticoagulation (Table 14–22). In the first year after discontinuation of anticoagulation therapy, the frequency of recurrent VTE among individuals whose thrombosis occurred in the setting of a transient, major, reversible risk factor (such as surgery) is approximately 3% after completing 3 months of anticoagulation, compared with at least 8% for individuals whose thrombosis was unprovoked, and greater than 20% in patients with cancer. Men have a greater than twofold higher risk of recurrent VTE compared to women; recurrent PE is more likely to develop in patients with clinically apparent PE than in those with DVT alone and has a case fatality rate of nearly 10%; and proximal DVT has a higher recurrence risk than distal DVT.

1. Provoked versus unprovoked VTE—Patients with provoked VTE are generally treated with a minimum of 3 months of anticoagulation, whereas unprovoked VTE should prompt consideration of indefinite anticoagulation provided the patient is not at high risk for bleeding. Merely extending duration of anticoagulation beyond 3 months for unprovoked PE will not reduce risk of recurrence once anticoagulation is stopped; if anticoagulants are stopped after 3, 6, 12, or 18 months in such a patient, the risk of recurrence after cessation of therapy is similar. Individual risk stratification may help identify patients most likely to suffer recurrent disease and thus most likely to benefit

Table 14–19. Warfarin dosing adjustment guidelines for initiation of warfarin therapy.

Measurement Day	INR	Action
For Hospitalized Patients Newly Starting Therapy		
Day 1		5 mg (2.5 or 7.5 mg in select populations[1])
Day 2	< 1.5	Continue dose
	≥ 1.5	Decrease or hold dose[2]
Day 3	≤ 1.2	Increase dose[2]
	> 1.2 and < 1.7	Continue dose
	≥ 1.7	Decrease dose[2]
Day 4 until therapeutic	Daily increase < 0.2 units	Increase dose[2]
	Daily increase 0.2–0.3 units	Continue dose
	Daily increase 0.4–0.6 units	Decrease dose[2]
	Daily increase ≥ 0.7 units	Hold dose
For Outpatients Newly Starting Therapy		
Measure PT/INR on Day 1	Baseline	Start treatment with 2–7.5 mg
Measure PT/INR on Day 3–4	< 1.5	Increase weekly dose by 5–25%
	1.5–1.9	No dosage change
	2.0–2.5	Decrease weekly dose by 25–50%
	> 2.5	Decrease weekly dose by 50% or HOLD dose
Measure PT/INR on Day 5–7	< 1.5	Increase weekly dose by 10–25%
	1.5–1.9	Increase weekly dose by 0–20%
	2.0–3.0	No dosage change
	> 3.0	Decrease weekly dose by 10–25% or HOLD dose
Measure PT/INR on Day 8–10	< 1.5	Increase weekly dose by 15–35%
	1.5–1.9	Increase weekly dose by 5–20%
	2.0–3.0	No dosage change
	> 3.0	Decrease weekly dose by 10–25% or HOLD dose
Measure PT/INR on Day 11–14	< 1.6	Increase weekly dose by 15–35%
	1.6–1.9	Increase weekly dose by 5–20%
	2.0–3.0	No dosage change
	> 3.0	Decrease weekly dose by 5–20% or HOLD dose

[1]See text.
[2]In general, dosage adjustments should not exceed 2.5 mg or 50%.
Data from Kim YK et al. J Thromb Haemost. 2010;8:101. From Center for Health Quality, Outcomes, and Economic Research, VA Medical Center, Bedford, MA.

from ongoing anticoagulation therapy (see below). Normal D-dimer levels 1 month after cessation of anticoagulation are associated with lower recurrence risk, although some would argue not low enough to consider stopping anticoagulant therapy, particularly in men.

2. Risk scoring systems to guide therapy duration—The HERDOO2 risk scoring system uses BMI, age, D-dimer, and post-phlebitic symptoms to identify women at lower risk for recurrence after unprovoked VTE (https://www.mdcalc.com/herdoo2-rule-discontinuing-anticoagulation-unprovoked-vte). The Vienna Prediction Model, a simple scoring system based on age, sex, D-dimer, and location of thrombosis, can help estimate an individual's recurrence risk to guide duration of therapy decisions.

3. Cancer-related VTE—LMWH has been the mainstay of treatment for cancer-related VTE based on lower VTE recurrence in cancer patients treated with dalteparin compared with warfarin. Studies have also shown that DOACs (edoxaban, rivaroxaban, and apixaban) are at least as effective as LMWH for VTE treatment. The use of edoxaban and rivaroxaban is associated with increased bleeding, though, particularly for patients with GI cancer.

Table 14–20. Warfarin-dosing adjustment guidelines for patients receiving long-term therapy, with target INR 2–3.

Patient INR	Weekly Dosing Change	
	Dose Change	Follow-Up INR
≤ 1.5	Increase by 10–15%	Within 1 week
1.51–1.79	If falling or low on two or more occasions, increase weekly dose by 5–10%.	7–14 days
1.80–2.29	Consider not changing the dose unless a consistent pattern has been observed.	7–14 days
2.3–3.0 (in range)	No change in dosage.	28 days (42 days if INR in range three times consecutively)
3.01–3.20	Consider not changing the dose unless a consistent pattern has been observed.	7–14 days
3.21–3.69	Do not hold warfarin. If rising or high on two or more occasions, decrease weekly dose by 5–10%.	7–14 days
3.70–4.99	Hold warfarin for 1 day and decrease weekly dose by 5–10%.	Within 1 week, sooner if clinically indicated
5.0–8.99	Hold warfarin. Clinical evaluation for bleeding. When INR is therapeutic, restart at lower dose (decrease weekly dose by 10–15%). Check INR at least weekly until stable. Consider vitamin K if bleeding risk is high (see Table 14–21).	Within 1 week, sooner if clinically indicated, then weekly until stabilized
≥ 9	See Table 14–21	

From Center for Health Quality, Outcomes, and Economic Research, VA Medical Center, Bedford, MA. Data from Kim YK et al. J Thromb Haemost. 2010;8:101. See also Van Spall HE et al. Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between centers and countries: an analysis of patients receiving warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial. Circulation. 2012;126:2309.

The International Society for Thrombosis and Haemostasis suggests use of the oral factor Xa inhibitors apixaban, rivaroxaban, or edoxaban for cancer patients with a diagnosis of acute VTE, no drug-drug interactions, and a low risk of bleeding. However, the use of LMWH is suggested for those with a high risk of bleeding, including patients with luminal GI cancers with an intact primary tumor and those at risk for bleeding from the genitourinary or GI tract. For patients with intracranial malignancy and VTE, bleeding risk depends on tumor type (primary versus metastatic) and other characteristics; whenever possible, interdisciplinary consultation is recommended to help determine risk of initiating anticoagulation. DOACs do not appear to confer higher bleeding risk compared to LMWH in patients with brain tumors. Clinicians must be aware that chemotherapeutic agents may interact with DOACs and their use should be avoided in cases of potential interactions because there is no easily accessible and reliable way to measure the anticoagulant effect of DOACs.

4. Thrombophilia workup in determining duration— Laboratory workup for thrombophilia is not recommended routinely for determining duration of therapy because clinical presentation is a much stronger predictor of recurrence risk. The workup may be pursued in patients younger than 50 years, with a strong family history, with a clot in unusual locations, or with recurrent thromboses (Table 14–23). In addition, a workup for thrombophilia may be considered in women of childbearing age in whom results may influence fertility and pregnancy outcomes and management or in those patients in whom results will influence duration of therapy. An important hypercoagulable state to identify is antiphospholipid syndrome because these patients have a marked increase in recurrence rates, are at risk for both arterial and venous disease, in general receive bridge therapy during any interruption of anticoagulation, and should not receive DOACs as first-line antithrombotic therapy due to increased arterial events compared to warfarin. Due to effects of anticoagulants and acute thrombosis on many of the tests, the thrombophilia workup should be delayed in most cases until at least 3 months after the acute event, if indicated at all (Table 14–24). The benefit of anticoagulation must be weighed against the bleeding risks posed, and the benefit-risk ratio should be assessed at the initiation of therapy, at 3 months, and then at least annually in any patient receiving prolonged anticoagulant therapy. Bleeding risk scores, such as the Riete score (https://www.mdcalc.com/riete-score-risk-hemorrhage-pulmonary-embolism-treatment) have been developed to estimate risk of these complications. Their performance, however, may not offer any advantage over a clinician's subjective assessment, particularly in older individuals. Consideration of bleeding risk is of particular importance when identifying candidates for extended duration therapy for treatment of unprovoked VTE; defined courses should be considered for patients at high bleeding risk.

D. Secondary Prevention

Antithrombotic therapy for secondary prevention offered after the initial 3–6 months of treatment should be considered in patients with VTE that is not majorly provoked; it is most compelling for those with unprovoked VTE. For most patients who continue to take a DOAC to prevent recurrence, the dose can be reduced to prophylactic intensity after the initial 6 months of therapy. In patients deemed poor candidates for ongoing DOAC or warfarin use but who warrant some secondary prevention, low-dose (81–100 mg) aspirin may be used; however, this will

Table 14–21. American College of Chest Physicians evidence-based clinical practice guidelines for the management of supratherapeutic INR.

Clinical Situation	INR	Recommendations
No significant bleed	Above therapeutic range but < 5.0	• Lower dose or omit dose (see Table 14–20). • Monitor more frequently and resume at lower dose when INR falls within therapeutic range (if INR only slightly above range, may not be necessary to decrease dose)
	≥ 5.0 but < 9.0	• Hold next 1–2 doses • Monitor more frequently and resume therapy at lower dose (see Table 14–20) when INR falls within therapeutic range • *Patients at high risk for bleeding*[1]: Hold warfarin and consider giving vitamin K_1 1–2.5 mg orally; check INR in 24–48 hour to ensure response to therapy
	≥ 9.0	• Hold warfarin
		• Vitamin K_1 2.5–5 mg orally • Monitor frequently and resume therapy at lower dose when INR within therapeutic range
Serious/life-threatening bleed		• Hold warfarin and give 10 mg vitamin K by slow intravenous infusion supplemented by FFP, PCC, or recombinant factor VIIa (PCC preferred)

[1]Patients at higher risk for bleeding include elderly people, and conditions that increase the risk of bleeding include kidney disease, hypertension, falls, liver disease, and history of GI or genitourinary bleeding.
FFP, fresh frozen plasma; PCC, prothrombin complex concentrate.

provide far less reduction in risk of recurrent VTE with similar bleeding risk.

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Table 14–22. Duration of treatment of VTE.

Scenario	Suggested Duration of Therapy	Comments
Provoked by major transient risk factor (eg, major surgery, major trauma, major hospitalization)	3 months	VTE prophylaxis upon future exposure to transient risk factor
Unprovoked	At least 3 months; consider indefinite if bleeding risk allows	May individually risk-stratify for recurrence with D-dimer, clinical risk scores, and clinical presentation Consider transition to DOAC secondary prevention dose after initial treatment period
Recurrent unprovoked	Indefinite	If recurrent despite therapeutic anticoagulation, consider hematology consultation for further evaluation and guidance
Cancer-related	≥ 3–6 months or as long as cancer is active, whichever is longer	LMWH or carefully selected DOAC recommended for initial treatment (see Table 14–16)
Underlying significant thrombophilia (eg, antiphospholipid antibody syndrome, antithrombin deficiency, protein C deficiency, protein S deficiency, ≥ two concomitant thrombophilic conditions)	Indefinite	To avoid false positives, consider delaying investigation for laboratory thrombophilia until 3 months after event

LMWH, low-molecular-weight heparin; VTE, venous thromboembolic disease.

Table 14–23. Candidates for thrombophilia workup if results will influence management.

Patients < 50 years of age
Strong family history of VTE
Clot in unusual locations
Recurrent thromboses
Women of childbearing age
Suspicion for APS (avoid DOACs if APS is strongly suspected or confirmed)

APS, antiphospholipid syndrome; VTE, venous thromboembolism.

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E. Thrombolytic Therapy

1. Thrombolytic therapy for high risk, massive PE— Anticoagulation alone is appropriate treatment for most patients with PE. However, patients with high-risk, massive PE (defined as PE causing sustained hypotension [systolic blood pressure greater than 90 mm Hg]) or requirement for inotropic support) have an in-hospital mortality rate that approaches 30% and, absent contraindications (Table 14–25), require immediate thrombolysis in combination with anticoagulation (Table 14–26).

2. Thrombolytic therapy for intermediate-risk, submassive PE— Systemic thrombolytic therapy has been used in carefully selected patients with intermediate-risk, submassive PE (defined as PE without hemodynamic instability but with evidence of right ventricular compromise and myocardial injury). Thrombolysis in this cohort decreases risk of hemodynamic compromise but increases the risk of major hemorrhage and stroke. A lower dose of alteplase (tPA) commonly used for PE treatment (50 mg rather than 100 mg) has been evaluated in small trials. Catheter-directed therapy for acute PE may be considered for high-risk or intermediate-risk PE when systemic thrombolysis has failed or as an alternative to systemic thrombolytic therapy.

3. Thrombolytic therapy for other indications— In patients with large proximal iliofemoral DVT, data from randomized controlled trials are limited on the benefit of catheter-directed thrombolysis in addition to treatment with anticoagulation but do show increased risk of major bleeding. Thrombolytic therapy should be reserved for patients at the highest risk for limb ischemia from extensive acute thrombosis.

Table 14–24. Laboratory evaluation of thrombophilia.

Hypercoagulable State	When to Suspect	Laboratory Workup	Influence of Anticoagulation and Acute Thrombosis
Antiphospholipid antibody syndrome	Unexplained DVT/PE CVA/TIA before age 50 years Recurrent thrombosis (despite anticoagulation) Thrombosis at an unusual site Arterial and venous thrombosis Livedo reticularis, Raynaud phenomenon, thrombocytopenia, recurrent early pregnancy loss	Anti-cardiolipin IgG and/or IgM medium or high titer (ie, > 40 GPL or MPL, or > the 99th percentile)[1] Anti-beta-2 glycoprotein I IgG and/or IgM medium or high titer (> the 99th percentile)[1] Lupus anticoagulant[1]	Lupus anticoagulant can be falsely positive or falsely negative on anticoagulation
Protein C, S, antithrombin deficiencies	Thrombosis < 50 years of age with family history of VTE	Screen with protein C activity, free protein S, antithrombin activity[2]; if free protein S is normal, check protein S activity	Acute thrombosis can result in decreased protein C, S and antithrombin activity. Warfarin can decrease protein C and S activity; heparin can decrease antithrombin activity. DOACs can increase protein C, S, and antithrombin activity
Factor V Leiden, prothrombin gene mutation	Thrombosis on OCPs, cerebral vein thrombosis, DVT/PE in White population	PCR for factor V Leiden or prothrombin gene mutation	No influence
Hyperhomocysteinemia		Fasting homocysteine	No influence

[1]Detected on two occasions not < 12 weeks apart.
[2]Nephrotic syndrome and liver disease can reduce protein C, protein S, and antithrombin; pregnancy causes decreased free protein S.
CVA/TIA, cerebrovascular accident/transient ischemic attack; OCPs, oral contraceptives; VTE, venous thromboembolism.

Table 14–25. Contraindications to thrombolytic therapy for PE.

	Contraindication		
	Absolute	**Major**	**Relative**
American Heart Association	Previous intracranial hemorrhage Structural intracranial disease Ischemic stroke within 3 months Suspected aortic dissection Active bleeding or bleeding diathesis Recent surgery encroaching on the spinal canal or brain Recent closed-head or facial trauma with radiographic evidence of bony fracture or brain injury		Age > 75 years Anticoagulant therapy Pregnancy Noncompressible vascular punctures Traumatic or prolonged CPR (> 10 minutes) Recent internal bleeding (within 2–4 weeks) Chronic, poorly controlled hypertension Systolic BP > 180 mm Hg or diastolic BP > 110 mm Hg Dementia Ischemic stroke > 3 months ago Major surgery within 3 weeks
European Society of Cardiology	Previous hemorrhagic stroke or stroke of unknown origin CNS damage or neoplasms Ischemic stroke within 6 months GI bleeding within 1 month Recent major trauma, surgery, or head injury in the preceding 3 weeks Known bleeding risk		TIA in preceding 6 months Anticoagulant therapy Pregnancy Noncompressible puncture site Traumatic resuscitation Active peptic ulcer disease Infective endocarditis Refractory hypertension (systolic BP > 180 mm Hg) Advanced liver disease
American College of Chest Physicians		Previous intracranial hemorrhage Structural intracranial disease Ischemic stroke within 3 months Active bleeding Bleeding diathesis Recent brain or spinal surgery Recent head trauma with fracture or brain injury	Age > 75 years Anticoagulant therapy Pregnancy Recent invasive procedure Traumatic CPR Recent non-intracranial bleeding Pericarditis or pericardial fluid Systolic BP > 180 mm Hg or diastolic BP > 110 mm Hg Weight < 60 kg Ischemic stroke > 3 months ago Recent surgery Diabetic retinopathy Female Black race

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F. Nonpharmacologic Therapy

1. Graduated compression stockings—Graduated compressions stockings may provide symptomatic relief to selected patients with ongoing swelling but do not reduce risk of postthrombotic syndrome at 6 months. They are contraindicated in patients with peripheral vascular disease.

2. Inferior vena caval (IVC) filters—There is a paucity of data to support the use of permanent or retrievable IVC filters for the prevention of PE in any clinical scenario. There are two randomized, controlled trials of IVC filters for prevention of PE. In the first study, patients with documented DVT received full- intensity, time-limited anticoagulation with or without placement of a permanent IVC filter. Patients with permanent IVC filters had a lower rate

Table 14–26. Thrombolytic regimens for acute PE.

Alteplase[1]		Streptokinase[1]		Urokinase[1]		Reteplase	Tenecteplase
Classical Regimen	Accelerated Regimen	Classical Regimen	Accelerated Regimen	Classical Regimen	Accelerated Regimen		
100 mg infusion over 2 hour	0.6 mg/kg (up to 50 mg) bolus over 15 minutes	250,000 IU bolus over 30 minutes, followed by 100,000 IU/hour over 12–24 hours	1.5 million IU infusion over 2 hours	4400 IU/kg bolus followed by 4400 IU/kg/hour infusion over 12–24 hours	3 million IU infusion over 2 hours	Two boluses of 10 units given 30 minutes apart	Weight-based bolus over 5 s: < 60 kg: 30 mg ≥ 60 to < 70 kg: 35 mg ≥ 70 to < 80 kg: 40 mg ≥ 80 to < 90 kg: 45 mg ≥ 90 kg: 50 mg

[1]FDA approved thrombolytic for PE.

Reproduced with permission from Kaplovitch E, Shaw JR, Douketis J. Thrombolysis in pulmonary embolism: an evidence-based approach to treating life-threatening pulmonary emboli. Crit Care Clin. 2020;36(3):465–480.

of nonfatal asymptomatic PE at 12 days but an increased rate of DVT at 2 years. In the second study, patients with symptomatic PE and residual proximal DVT plus at least one additional risk factor for severity received full intensity anticoagulation with or without a retrievable IVC filter. IVC filter use did not reduce the risk of symptomatic recurrent PE at 3 months. While IVC filters were once commonly used to prevent VTE recurrence in the setting of anticoagulation failure, many experts now recommend switching to an alternative agent or increasing the intensity of the current anticoagulant regimen instead. Most experts agree with placement of a retrievable IVC filter in patients with acute proximal DVT or PE and an absolute contraindication to anticoagulation; evidence to support this practice, however, is lacking. The remainder of the indications (submassive/intermediate-risk PE, free-floating iliofemoral DVT, perioperative risk reduction) are controversial. Whenever possible, the filter should be removed once anticoagulation has been started and has been shown to be tolerated. Rates of IVC filter retrieval are very low, often due to failure to arrange for removal. Thus, if a device is placed, removal should be arranged at the time of device placement.

Complications of IVC filters include local thrombosis, tilting, migration, fracture, and inability to retrieve the device. When considering placement of an IVC filter, it is best to consider both short- and long-term complications, since devices intended for removal may become permanent. To improve patient safety, institutions should develop systems that guide appropriate patient selection for IVC filter placement, tracking, and removal.

3. Mechanical embolectomy—Patients with high-risk VTE and very high bleeding risk may be considered for mechanical embolectomy if local expertise and resources are available.

When to Refer

- Presence of large iliofemoral VTE, unprovoked upper extremity DVT, IVC thrombosis, portal vein thrombosis, or Budd-Chiari syndrome for consideration of catheter-directed thrombolysis.
- High-risk PE for urgent embolectomy or catheter-directed therapies.
- Intermediate-risk PE if considering thrombolysis.
- History of HIT or prolonged PTT plus kidney failure for alternative anticoagulation regimens.
- Consideration of IVC filter placement.
- Clots in unusual locations (eg, renal, hepatic, or cerebral vein), or simultaneous arterial and venous thrombosis, to assess possibility of a hypercoagulable state.
- Recurrent VTE while receiving therapeutic anticoagulation.

When to Admit

- Documented or suspected intermediate- or high-risk PE, low-risk PE at high risk for bleeding, poor candidate for outpatient treatment.
- DVT with poorly controlled pain, high bleeding risk, or concerns about follow-up.
- Large iliofemoral DVT for consideration of thrombolysis.
- Acute PE/DVT and absolute contraindication to anticoagulation for IVC filter placement.
- Venous thrombosis despite therapeutic anticoagulation.
- Suspected Paget-Schroetter syndrome (spontaneous upper extremity thrombosis related to thoracic outlet syndrome).

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PRIMARY VTE PREVENTION & TREATMENT IN SEVERE COVID-19

Patients hospitalized with severe COVID-19 have an increased incidence of thrombotic complications, including venous (DVT, PE) and arterial (stroke, limb occlusion) events.

Although the reasons for this hypercoagulability are not yet well understood, the profound systemic inflammatory response associated with severe COVID-19 is thought to play a role.

Clinical Findings

While the hypercoagulability in COVID-19 resembles DIC, laboratory and clinical findings are somewhat different. Laboratory findings in patients with severe COVID-19 may include markedly elevated D-dimer and modestly prolonged prothrombin time. However, patients with COVID-19 tend to have elevated fibrinogen levels; thrombocytopenia is rare and nonsevere; and bleeding complications are unusual. Thrombosis in patients with COVID-19 is associated with a poor prognosis and often occurs despite standard pharmacologic prophylaxis.

Risk Stratification & Initial Prognostication in Severe COVID-19

Given the prevalence and prognostic value of abnormal laboratory findings at presentation, patients hospitalized with COVID-19 should have PT/INR, PTT, D-dimers, and fibrinogen measured at presentation. Serial monitoring should be considered even in patients who are otherwise clinically stable. Worsening laboratory parameters during hospitalization should prompt consideration of transfer to a higher level of care and heightened clinical suspicion for thrombosis.

VTE Prophylaxis for Severe COVID-19

In the absence of strong contraindications, all patients hospitalized with COVID-19 should receive pharmacologic VTE prophylaxis. LMWH is preferred over unfractionated heparin to minimize staff exposure and the chance of HIT.

For patients with a prior history of VTE who take an oral anticoagulant for secondary prevention at the time of admission, transition to LMWH should be considered due to its shorter half-life and potential anti-inflammatory properties.

Some patients who are hospitalized in the acute care setting with COVID-19, who have very elevated D-dimer values (over 4 times the upper limit of normal) and require supplemental oxygen, and who have *low* bleeding risk, may benefit from therapeutic dosing of anticoagulation. Patients who are critically ill in ICUs have not been shown to benefit from therapeutic dosing. At this time, there is also no clear benefit from VTE prophylaxis for patients with COVID-19 who do not require hospitalization. Trials are ongoing to evaluate the benefit of pharmacologic VTE prophylaxis with DOACs for COVID-19 patients following hospital discharge.

For updated recommendations regarding pharmacologic dosing and post-discharge prophylaxis, refer to professional society guidance (links at end of this section) since guidance in this area is evolving rapidly.

Diagnosis & Management of VTE in Severe COVID-19

Logistical challenges complicate the diagnosis of thromboembolism in patients with COVID-19 due to patient instability and risks of staff exposures. D-dimers are generally elevated in hospitalized patients who have COVID-19. A substantial increase in D-dimers may suggest COVID-19–associated coagulopathy with or without thrombotic events. Clinicians should remain vigilant for signs and symptoms of thrombosis and consider obtaining surveillance laboratory testing at least every 3–4 days with low threshold for imaging. Ideally, thrombosis should be confirmed radiographically, but in situations where these studies cannot safely be obtained and clinical suspicion is very high, empiric treatment may be considered.

Guidance from the Anticoagulation Forum (https://acforum.org/web/), the International Society for Thrombosis and Haemostasis (https://academy.isth.org/isth/#!*menu=8*browseby=2*sortby=1*label=19794), and the American Society for Hematology (https://www.hematology.org/covid-19) is evolving and should be frequently consulted.

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Gastrointestinal Disorders

Kenneth R. McQuaid, MD

15

SYMPTOMS & SIGNS OF GI DISEASE

DYSPEPSIA

ESSENTIALS OF DIAGNOSIS

- Predominant epigastric pain or discomfort.
- May be associated with heartburn, nausea, postprandial fullness, or vomiting.
- Endoscopy is warranted in all patients age 60 years or older and selected younger patients with "alarm" features.
- In all other patients, testing for *Helicobacter pylori* is recommended; if positive, antibacterial treatment is given.
- Patients who are *H pylori* negative or do not improve after *H pylori* eradication should be prescribed a trial of empiric PPI therapy.
- Patients with persistent symptoms should be offered a trial of a tricyclic antidepressant.

General Considerations

Dyspepsia refers to acute, chronic, or recurrent pain or discomfort centered in the upper abdomen. Predominant epigastric pain that is present for at least 1 month is clinically relevant. Dyspepsia occurs in 10–20% of the adult population and accounts for 3% of general medical office visits. The epigastric pain may be associated with heartburn, nausea, postprandial fullness, or vomiting. Heartburn (retrosternal burning) should be distinguished from dyspepsia. When heartburn is the dominant complaint, gastroesophageal reflux is nearly always present.

Etiology

A. Food or Drug Intolerance

Acute, self-limited "indigestion" may be caused by overeating, eating too quickly, eating high-fat foods, eating during stressful situations, or drinking too much alcohol or coffee. Prescription and nonprescription medications should be carefully reviewed since many may cause dyspepsia.

B. Functional Dyspepsia

Functional dyspepsia refers to dyspepsia for which no organic etiology has been determined by endoscopy or other testing. This is the most common cause of *chronic* dyspepsia, accounting for up to 75% of patients. Symptoms may arise from a complex interaction of increased visceral afferent sensitivity, gastric delayed emptying or impaired accommodation to food or psychosocial stressors or symptoms may develop de novo following an enteric infection. Although benign, these chronic symptoms may be difficult to treat.

C. Luminal GI Tract Dysfunction

Peptic ulcer disease is present in 5–15% of patients with dyspepsia. GERD is present in up to 20% of patients with dyspepsia, even without significant heartburn. Gastric or esophageal cancer is identified in less than 1%; cancer is extremely rare in persons under age 60 years with uncomplicated dyspepsia. Other causes include gastroparesis (especially in diabetes mellitus) and parasitic infection (*Giardia, Strongyloides, Anisakis*).

D. *Helicobacter pylori* Infection

Chronic gastric infection with *H pylori* is an important cause of peptic ulcer disease but may cause dyspepsia in a subset of patients in the absence of peptic ulcer disease.

E. Pancreatic Disease

Pancreatic carcinoma and chronic pancreatitis may cause chronic epigastric pain, but it is more severe, sometimes radiates to the back, and usually is associated with anorexia, rapid weight loss, steatorrhea, or jaundice.

F. Biliary Tract Disease

The abrupt onset of epigastric or right upper quadrant pain due to cholelithiasis or choledocholithiasis should be readily distinguished from dyspepsia.

G. Other Conditions

Diabetes mellitus, thyroid disease, CKD, myocardial ischemia, intra-abdominal malignancy, gastric volvulus or paraesophageal hernia, chronic gastric or intestinal ischemia, and pregnancy are sometimes accompanied by acute or chronic epigastric pain or discomfort.

Clinical Findings

A. Symptoms and Signs

Given the nonspecific nature of dyspeptic symptoms, the history has limited diagnostic utility. It should clarify the chronicity, location, and quality of the epigastric pain, and its relationship to meals. The pain may be accompanied by one or more upper abdominal symptoms including postprandial fullness, heartburn, nausea, or vomiting. Concomitant weight loss, persistent vomiting, constant or severe pain, progressive dysphagia, hematemesis, or melena warrants endoscopy or abdominal CT imaging. Potentially offending medications and excessive alcohol use should be identified and discontinued if possible. The patient should be asked about a family history of upper GI cancer. The patient's reason for seeking care should be determined. Recent changes in employment, marital discord, physical and sexual abuse, anxiety, depression, and fear of serious disease may all contribute to the development and reporting of symptoms. Patients with functional dyspepsia often are younger, report a variety of abdominal and extragastrointestinal complaints, show signs of anxiety or depression, or have used psychotropic medications.

The symptom profile alone does not differentiate between functional dyspepsia and organic GI disorders. Based on the clinical history alone, primary care clinicians misdiagnose nearly half of patients with peptic ulcers or gastroesophageal reflux.

The physical examination is rarely helpful. Signs of serious organic disease such as weight loss, organomegaly, abdominal mass, or fecal occult blood must be further evaluated.

B. Laboratory Findings

In patients younger than age 60 with uncomplicated dyspepsia (in whom gastric cancer is rare), a noninvasive test for *H pylori* (urea breath test, fecal antigen test) should be performed first. Although serologic tests are inexpensive, performance characteristics are poor in low-prevalence populations, whereas breath and fecal antigen tests have 95% accuracy. If *H pylori* breath test or fecal antigen test results are negative in a patient not taking NSAIDs, peptic ulcer disease is virtually excluded. In patients older than age 60 years, initial laboratory work should include a CBC, serum electrolytes, liver enzymes, calcium, and thyroid function tests but the cost-effectiveness of such studies is uncertain.

C. Upper Endoscopy

Upper endoscopy is mainly indicated to look for upper gastric or esophageal malignancy in *all* patients over age 60 years with new-onset dyspepsia (in whom there is increased malignancy risk). In patients under age 60, the risk of malignancy is less than 1% so recent guidelines recommend against routine endoscopy for most younger patients—except those with prominent "alarm" features, such as progressive weight loss, rapidly progressive dysphagia, persistent vomiting, evidence of bleeding or iron deficiency anemia, palpable abdominal mass, or a family history of upper GI cancer. For patients born in regions in which there is a higher incidence of gastric cancer, such as Central or South America, China and Southeast Asia, or Africa, an age threshold of 45 years may be more appropriate.

Endoscopy may also be warranted when symptoms fail to respond to initial empiric management or when frequent symptom relapse occurs after discontinuation of empiric therapy.

D. Other Tests

In patients with refractory symptoms or progressive weight loss, antibodies for celiac disease or stool testing for ova and parasites or *Giardia* antigen, fat, or elastase may be considered. Abdominal imaging (ultrasonography or CT) is performed only when pancreatic, biliary tract, vascular disease, or volvulus is suspected. Gastric emptying studies may be useful in patients with recurrent nausea and vomiting who have not responded to empiric therapies.

Treatment

Initial empiric treatment is recommended for patients who are younger than age 60 years and who lack severe or worrisome "alarm" features that warrant further testing with endoscopy or abdominal imaging. Those whose symptoms do not to respond to or relapse after empiric treatment should undergo upper endoscopy with subsequent treatment directed at the specific disorder identified (eg, peptic ulcer, gastroesophageal reflux, cancer). When endoscopy is performed, gastric biopsies should be obtained to test for *H pylori* infection. If infection is present, antibacterial treatment should be given.

A. Empiric Therapy

Patients younger than age 60 should be tested for *H pylori* and, if positive, treated for 14 days with an effective regimen (see Table 15–10). *H pylori* eradication therapy proves definitive for patients with underlying peptic ulcers and may improve symptoms in a small subset (less than 10%) of infected patients with functional dyspepsia.

H pylori–negative patients and patients with persistent dyspepsia after *H pylori* eradication most likely have functional dyspepsia or atypical GERD and should be treated with a PPI for 4 weeks. Meta-analysis of six randomized controlled trials reported symptom improvement in 50% of patients treated with a PPI versus 27% of those treated with a placebo. For patients who have symptom relapse after discontinuation of the PPI, intermittent or long-term PPI therapy may be considered.

B. Treatment of Functional Dyspepsia

Patients who have no significant findings on endoscopy as well as patients under age 60 who do not respond to *H pylori*

eradication or empiric PPI therapy are presumed to have functional dyspepsia. Patients with mild, intermittent symptoms may respond to reassurance and lifestyle or dietary changes. A food diary, in which patients record their food intake, symptoms, and daily events, may reveal dietary or psychosocial precipitants of pain. Herbal therapies (peppermint, caraway) may offer benefit with little risk of adverse effects.

Antisecretory drugs (PPIs or H_2-receptor antagonists) have demonstrated limited efficacy in the treatment of functional dyspepsia. A small number of patients (less than 10%) derive benefit from *H pylori* eradication therapy. Low doses of tricyclic antidepressants (eg, desipramine or nortriptyline, 25–50 mg orally at bedtime) benefit some patients, possibly by moderating visceral afferent sensitivity. Doses should be increased slowly to minimize side effects. SSRIs do not appear to be beneficial. Although some prokinetics have demonstrated modest improvement in global symptoms compared to placebo in controlled trials, the more effective agents are either not available in the United States (domperidone) or were removed from the market to due rare but serious adverse events (cisapride). Metoclopramide (5–10 mg three times daily) may improve symptoms but cannot be recommended for long-term use due to the risk of tardive dyskinesia.

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NAUSEA & VOMITING

Nausea is a vague, intensely disagreeable sensation of sickness or "queasiness" and is distinguished from anorexia. Vomiting often follows, as does retching (spasmodic respiratory and abdominal movements). Vomiting should be distinguished from regurgitation, the effortless reflux of liquid or food stomach contents; and from rumination, the chewing and swallowing of food that is regurgitated volitionally after meals.

The brainstem vomiting center is composed of a group of neuronal areas within the medulla that coordinate emesis. It may be stimulated by four sources of afferent input: (1) Afferent vagal fibers from the GI viscera are rich in serotonin 5-HT_3 receptors; these may be stimulated by biliary or GI distention, mucosal or peritoneal irritation, or infections. (2) Fibers of the vestibular system, which have high concentrations of histamine H_1 and muscarinic cholinergic receptors. (3) Higher CNS centers (amygdala); here, certain sights, smells, or emotional experiences may induce vomiting. (4) The chemoreceptor trigger zone, located outside the blood-brain barrier in the medulla, is rich in opioid, serotonin 5-HT_3, neurokinin 1 (NK_1), and dopamine D_2 receptors. This region may be stimulated by drugs and chemotherapeutic agents, toxins, hypoxia, uremia, acidosis, and radiation therapy. Although the causes of nausea and vomiting are many, a simplified list is provided in Table 15–1.

Clinical Findings

A. Symptoms and Signs

Acute symptoms without abdominal pain are typically caused by food poisoning, infectious gastroenteritis, drugs, or systemic illness. A 2021 prospective study of 1992 consecutive patients with COVID-19 hospitalized at 36 North American medical centers reports that 27% had nausea, 16% had vomiting, and 11% had abdominal pain. GI symptoms were mild in 74% and the initial manifestation of disease in 13%. Inquiry should be made into recent changes in medications, diet, other intestinal symptoms, or similar illnesses in family members. The acute onset of severe pain and vomiting suggests peritoneal irritation, acute gastric or intestinal obstruction, or pancreaticobiliary disease. Persistent vomiting suggests pregnancy, gastric outlet obstruction, gastroparesis, intestinal dysmotility, psychogenic disorders, and CNS or systemic disorders. Vomiting that occurs in the morning before breakfast is common with pregnancy, uremia, alcohol intake, and increased intracranial pressure. Inquiry should be made into use of cannabis products. Suspect cannabinoid hyperemesis syndrome in patients with prolonged use, especially in those who report compulsive showering or bathing. Vomiting immediately after meals strongly suggests bulimia or psychogenic causes. Vomiting of undigested food one to several hours after meals is characteristic of gastroparesis or a gastric outlet obstruction; physical examination may reveal a succussion splash. Patients with acute or chronic symptoms should be asked about neurologic symptoms (eg, headache, stiff neck, vertigo, and focal paresthesias or weakness) that suggest a CNS cause.

B. Special Examinations

With vomiting that is severe or protracted, serum electrolytes should be obtained to look for hypokalemia, azotemia, or metabolic alkalosis resulting from loss of gastric contents. Flat and upright abdominal radiographs or abdominal CT are obtained in patients with severe pain or suspicion of mechanical obstruction to look for free intraperitoneal air or dilated loops of small bowel. The cause of gastric outlet obstruction is best demonstrated by upper endoscopy, and the cause of small intestinal obstruction is best demonstrated by abdominal CT. Gastroparesis is confirmed by nuclear scintigraphic studies or ^{13}C-octanoic acid breath tests, which show delayed gastric emptying and either upper endoscopy or barium upper GI series showing no evidence of mechanical gastric outlet obstruction. Abnormal liver biochemical tests or elevated amylase or lipase suggest pancreaticobiliary disease, which may be investigated with an abdominal sonogram or CT scan. CNS causes are best evaluated with either head CT or MRI.

Table 15–1. Causes of nausea and vomiting.

Visceral afferent stimulation	**Mechanical obstruction** Gastric outlet obstruction: peptic ulcer disease, malignancy, gastric volvulus Small intestinal obstruction: adhesions, hernias, volvulus, Crohn disease, carcinomatosis **Dysmotility** Gastroparesis: diabetic, postviral, postvagotomy Small intestine: systemic sclerosis (scleroderma), amyloidosis, chronic intestinal pseudo-obstruction, familial myoneuropathies **Peritoneal irritation** Peritonitis: perforated viscus, appendicitis, spontaneous bacterial peritonitis **Infections** Viral gastroenteritis: Norwalk agent, rotavirus, COVID-19 "Food poisoning": toxins from *Bacillus cereus, Staphylococcus aureus, Clostridium perfringens* Acute systemic infections **Hepatobiliary or pancreatic disorders** Acute or chronic pancreatitis Cholecystitis or choledocholithiasis **Topical GI irritants** Alcohol, NSAIDs, oral antibiotics **Postoperative** **Other** Cardiac disease: acute MI, heart failure Urologic disease: stones, pyelonephritis Vascular: chronic mesenteric ischemia, superior mesenteric artery syndrome
Vestibular disorders	**Vestibular disorders** Labyrinthitis, Ménière syndrome, motion sickness
CNS disorders	**Increased intracranial pressure** CNS tumors, subdural or subarachnoid hemorrhage **Migraine** **Cyclical vomiting syndrome** **Infections** Meningitis, encephalitis **Psychogenic** Anticipatory vomiting, anorexia nervosa and bulimia, psychiatric disorders
Irritation of chemoreceptor trigger zone	**Antitumor chemotherapy** **Medications and drugs** Opioids Marijuana Anticonvulsants Antiparkinsonism medications Beta-blockers, antiarrhythmics, digoxin Oral contraceptives Cholinesterase inhibitors Diabetes medications (metformin, acarbose, pramlintide, exenatide) **Radiation therapy** **Systemic disorders** Diabetic ketoacidosis Uremia Adrenocortical crisis Parathyroid disease Hypothyroidism Pregnancy Paraneoplastic syndrome

Complications

Complications include dehydration, hypokalemia, metabolic alkalosis, aspiration, rupture of the esophagus (Boerhaave syndrome), and bleeding secondary to a mucosal tear at the gastroesophageal junction (Mallory-Weiss syndrome).

Treatment

A. General Measures

Most causes of acute vomiting are mild, self-limited, and require no specific treatment. Patients should ingest clear liquids (broths, tea, soups, carbonated beverages) and

small quantities of dry foods (soda crackers). Ginger may be an effective nonpharmacologic treatment. For more severe acute vomiting, hospitalization may be required. Patients unable to eat and losing gastric fluids may become dehydrated, resulting in hypokalemia with metabolic alkalosis. Intravenous 0.45% saline solution with 20 mEq/L of potassium chloride is given in most cases to maintain hydration. A nasogastric suction tube for gastric or mechanical small bowel obstruction improves patient comfort and permits monitoring of fluid loss.

B. Antiemetic Medications

Medications may be given either to prevent or to control vomiting. Combinations of drugs from different classes may provide better control of symptoms with less toxicity in some patients. Table 15–2 outlines common antiemetic dosing regimens.

1. Serotonin 5-HT$_3$-receptor antagonists—Ondansetron, granisetron, and palonosetron are effective in preventing chemotherapy- and radiation-induced emesis when initiated prior to treatment; dolasetron has been discontinued in the United States. Due to its prolonged half-life and internalization of the 5-HT$_3$-receptor, palonosetron is superior to other 5-HT$_3$-receptor antagonists for the prevention of acute and delayed chemotherapy-induced emesis from moderately or highly emetogenic chemotherapeutic regimens. Although 5-HT$_3$-receptor antagonists are effective as single agents for the prevention of chemotherapy-induced nausea and vomiting, their efficacy is enhanced by combination therapy with a corticosteroid (dexamethasone)

Table 15–2. Common antiemetic dosing regimens.

	Dosage	Route
Serotonin 5-HT$_3$ Antagonists		
Ondansetron	Doses vary: 4–8 mg for postoperative nausea and vomiting 8 mg single dose IV or 8 mg twice daily orally for moderately or highly emetogenic chemotherapy	Intravenously, orally Intravenously, orally
Granisetron	1 mg once daily 1–2 mg once daily	Intravenously Orally
Palonosetron	0.25 mg once as a single dose 30 minutes before start of chemotherapy 0.5 mg once as single dose	Intravenously Orally
Corticosteroids		
Dexamethasone	4–12 mg once pre-induction for prevention of postoperative nausea and vomiting 8 mg once daily for chemotherapy	Intravenously, orally Intravenously, orally
Dopamine Receptor Antagonists		
Metoclopramide	10–20 mg or 0.5 mg/kg every 6–8 hours 10–20 mg every 6–8 hours	Intravenously Orally
Prochlorperazine	5–10 mg every 4–6 hours 25 mg suppository every 12 hours	Intravenously, intramuscularly, orally Per rectum
Promethazine	12.5–25 mg every 6–8 hours 25 mg every 6–8 hours	Intravenously, orally Per rectum
Trimethobenzamide	200 mg every 6–8 hours 250–300 mg every 6–8 hours	Orally Intravenously, orally
Olanzapine	5–10 mg once daily on days 1–4 for chemotherapy	
Neurokinin Receptor Antagonists[1]		
Aprepitant	125 mg once before chemotherapy; then 80 mg on days 1 and 2 after chemotherapy	Orally
Fosaprepitant	150 mg once 30 minutes before chemotherapy	Intravenously
Rolapitant	180 mg once before chemotherapy	Orally
Netupitant/palonosetron	Netupitant 300 mg/palonosetron 0.50 mg once before chemotherapy	Orally

[1]Neurokinin receptor antagonists are used solely for highly emetogenic chemotherapy regimens in combination with 5-HT$_3$ antagonists or dexamethasone or both.

and an NK_1-receptor antagonist. Serotonin antagonists increasingly are used for the prevention of postoperative nausea and vomiting because of increased restrictions on the use of other antiemetic agents (such as droperidol).

2. Corticosteroids—Corticosteroids (eg, dexamethasone) have antiemetic properties, but the basis for these effects is unknown. These agents enhance the efficacy of serotonin receptor antagonists for preventing acute and delayed nausea and vomiting in patients receiving moderately to highly emetogenic chemotherapy regimens.

3. Neurokinin receptor antagonists—Aprepitant, fosaprepitant, and rolapitant are highly selective antagonists for NK_1-receptors in the area postrema. They are used in combination with corticosteroids and serotonin antagonists for the prevention of acute and delayed nausea and vomiting with highly emetogenic chemotherapy regimens. Netupitant is another oral NK_1-receptor antagonist that is administered in a fixed-dose combination with palonosetron. Combined therapy with an NK_1 receptor antagonist prevents acute emesis in 80–90% and delayed emesis in more than 70% of patients treated with highly emetogenic regimens.

4. Dopamine antagonists—The phenothiazines, butyrophenones, and substituted benzamides (eg, prochlorperazine, promethazine) have antiemetic properties that are due to dopaminergic blockade as well as to their sedative effects. High doses of these agents are associated with antidopaminergic side effects, including extrapyramidal reactions and depression. With the advent of more effective and safer antiemetics, these agents are infrequently used, mainly in outpatients with minor, self-limited symptoms. The atypical antipsychotic agent olanzapine has potent antiemetic properties that may be mediated by blockade of both dopamine and serotonin neurotransmitters. In patients receiving highly emetic chemotherapy, the addition of olanzapine to a standard regimen (dexamethasone, serotonin-$5HT_3$ receptor antagonist, and NK_1- receptor antagonist) significantly reduces the risk of acute and delayed nausea and vomiting.

5. Antihistamines and anticholinergics—These drugs (eg, meclizine, dimenhydrinate, transdermal scopolamine) may be valuable in the prevention of vomiting arising from stimulation of the labyrinth, ie, motion sickness, vertigo, and migraines. They may induce drowsiness. A combination of oral vitamin B_6 and doxylamine is recommended by the American College of Obstetricians and Gynecologists as first-line therapy for nausea and vomiting during pregnancy.

6. Cannabinoids—Marijuana has been used widely as an appetite stimulant and antiemetic. Some states allow the use of medical marijuana with a clinician's certification. Strains of medical marijuana with different proportions of various naturally occurring cannabinoids (primarily THC and cannabidiol [CBD]) can be chosen to minimize its psychoactive effects. Excessive cannabinoid may cause nausea, vomiting, and abdominal pain (cannabinoid hyperemesis syndrome), which may be temporarily relieved with hot showers or bathing.

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HICCUPS

Though usually a benign and self-limited annoyance, hiccups may be persistent and a sign of serious underlying illness. In patients on mechanical ventilation, hiccups can trigger a full respiratory cycle and result in respiratory alkalosis.

Causes of benign, self-limited hiccups include gastric distention (carbonated beverages, air swallowing, overeating), sudden temperature changes (hot then cold liquids, hot then cold shower), alcohol ingestion, and states of heightened emotion (excitement, stress, laughing). There are over 100 causes of recurrent or persistent hiccups due to GI, CNS, cardiovascular, and thoracic disorders. Persistent hiccups may be an atypical presentation of COVID-19.

Clinical Findings

Evaluation of the patient with persistent hiccups should include a detailed neurologic examination, serum creatinine, liver chemistry tests, and a chest radiograph. When the cause remains unclear, CT; MRI of the head, chest, and abdomen; upper endoscopy; and echocardiography may help.

Treatment

A number of simple remedies may be helpful in patients with acute benign hiccups. (1) Irritation of the nasopharynx by tongue traction, lifting the uvula with a spoon, catheter stimulation of the nasopharynx, or eating 1 teaspoon (tsp) (7 g) of dry granulated sugar. (2) Interruption of the respiratory cycle by breath holding, Valsalva maneuver, sneezing, gasping (fright stimulus), or rebreathing into a bag. (3) Stimulation of the vagus by carotid massage. (4) Irritation of the diaphragm by holding knees to chest or by continuous positive airway pressure during mechanical ventilation. (5) Relief of gastric distention by belching or insertion of a nasogastric tube.

A number of drugs have been promoted as being useful in the treatment of hiccups. Chlorpromazine, 25–50 mg orally or intramuscularly, is most commonly used. Other agents reported to be effective include anticonvulsants (phenytoin, carbamazepine), benzodiazepines (lorazepam, diazepam), metoclopramide, baclofen, and gabapentin. For severe, intractable hiccups, phrenic nerve block, vagal

nerve stimulation and, occasionally, general anesthesia have been used with variable efficacy.

Adam E. A systematic review of the effectiveness of oral baclofen in the management of hiccups in adult palliative care patients. J Pain Palliat Care Pharmacother. 2020;34:43. [PMID: 31910072]
Prince G et al. Persistent hiccups as an atypical presenting complaint of COVID-19. Am J Emerg Med. 2020;38:1546. [PMID: 32345563]

CONSTIPATION

Constipation occurs in 15% of adults and up to one-third of older adults and is a common reason for seeking medical attention. It is more common in women. Older individuals are predisposed due to comorbid medical conditions, medications, poor eating habits, decreased mobility, and in some cases, inability to sit on a toilet (bed-bound patients). The first step in evaluating the patient is to determine what is meant by "constipation." Patients may define constipation as infrequent stools (fewer than three in a week), hard or lumpy stools, excessive straining, or a sense of incomplete evacuation. Table 15–3 summarizes the many causes of constipation, which are discussed below.

Table 15–3. Causes of constipation in adults.

Most common
Inadequate fiber or fluid intake
Poor bowel habits
Irritable bowel syndrome
Systemic disease
Endocrine: hypothyroidism, hyperparathyroidism, diabetes mellitus
Metabolic: hypokalemia, hypercalcemia, uremia, porphyria
Neurologic: Parkinson disease, multiple sclerosis, sacral nerve damage (prior pelvic surgery, tumor), paraplegia, autonomic neuropathy
Medications
Opioids
Diuretics
Calcium channel blockers
Anticholinergics
Psychotropics
Calcium and iron supplements
Clonidine
Cholestyramine
Structural abnormalities
Anorectal: rectal prolapse, rectocele, rectal intussusception, anorectal stricture, anal fissure, solitary rectal ulcer syndrome
Perineal descent
Colonic mass with obstruction: adenocarcinoma
Colonic stricture: radiation, ischemia, diverticulosis
Hirschsprung disease
Idiopathic megarectum
Slow colonic transit
Idiopathic: isolated to colon
Psychogenic
Eating disorders
Chronic intestinal pseudo-obstruction
Pelvic floor dyssynergia

Etiology

A. Primary Constipation

Most patients have constipation that cannot be attributed to any structural abnormalities or systemic disease. These patients may be further categorized as having normal colonic transit time, slow transit, or defecatory disorders (with or without slow colonic transit). Normal colonic transit time is approximately 35 hours; more than 72 hours is significantly abnormal. Slow colonic transit is commonly idiopathic (due to dysfunction of the enteric nervous system) but may be part of a generalized GI dysmotility syndrome. Normal defecation requires coordination between relaxation of the anal sphincter and pelvic floor musculature while abdominal pressure is increased. Patients with defecatory disorders (also known dyssynergic defecation)—women more often than men—have impaired relaxation or paradoxical contraction of the anal sphincter and/or pelvic floor muscles during attempted defecation that impedes the bowel movement. This problem may be acquired during childhood or adulthood. Patients may complain of excessive straining, sense of incomplete evacuation, need for digital manipulation, or adoption of a non-sitting (eg, standing) position during defecation. Patients with predominant complaints of abdominal pain or bloating with chronic idiopathic constipation are more appropriately given a diagnosis of irritable bowel syndrome (IBS) with constipation.

B. Secondary Constipation

Constipation may be caused by systemic disorders, medications, or obstructing colonic lesions. Systemic disorders that can cause constipation include neurologic gut dysfunction, myopathies, endocrine disorders, or electrolyte abnormalities (eg, hypercalcemia or hypokalemia); medication side effects are often responsible (eg, anticholinergics or opioids). Colonic lesions that obstruct fecal passage, such as neoplasms and strictures, are an uncommon cause but important in new-onset constipation. Such lesions should be excluded in patients older than age 50 years, in patients with "alarm" symptoms or signs (hematochezia, weight loss, anemia, or positive fecal occult blood tests [FOBT] or fecal immunochemical tests [FIT]), and in patients with a family history of colon cancer or inflammatory bowel disease. Defecatory difficulties also can be due to a variety of anorectal problems that impede or obstruct flow (perineal descent, rectal prolapse, rectocele), some of which may require surgery, and to Hirschsprung disease (usually suggested by lifelong constipation).

Clinical Findings

A. Symptoms and Signs

All patients should undergo a history and physical examination to distinguish primary from secondary causes of constipation. Physical examination should include digital rectal examination with assessment for anatomic abnormalities, such as anal stricture, rectocele, rectal prolapse, or

perineal descent during straining as well as assessment of pelvic floor motion during simulated defecation (ie, the patient's ability to "expel the examiner's finger"). Further diagnostic tests should be performed in patients with any of the following: signs of systemic disease, recent onset of constipation without apparent cause, "alarm" symptoms (hematochezia, weight loss, anemia, positive FOBT or FIT), family history of colon cancer or IBD, and age 45–50 years or older with no prior colonoscopy screening. These tests should include laboratory studies (CBC; serum electrolytes, calcium, glucose, and TSH) and a colonoscopy or flexible sigmoidoscopy.

B. Special Examinations

Patients with refractory constipation not responding to routine medical management warrant further diagnostic studies. Anorectal manometry including a balloon expulsion test should be performed first to evaluate for defecatory disorders. Inability to expel a balloon (attached to a 16F indwelling urinary catheter) filled with 50 mL of warm water within 1–2 minutes while sitting on a toilet is strongly suggestive of pelvic floor dyssynergia. Defecography to further assess pelvic floor function may be considered in selected patients. Subsequent colon transit studies are recommended only after defecatory disorders have been excluded. Colon transit time may be assessed by radiopaque markers, scintigraphy, or wireless motility capsule.

Treatment

A. Chronic Constipation

1. Dietary and lifestyle measures—Patients should be instructed on normal defecatory function and optimal toileting habits, including regular timing, proper positioning, and abdominal pressure. Adequate dietary fluid and fiber intake should be emphasized. Sorbitol-containing fruits and dried fruits (prunes, plums, apricots, cherries, mangos) and fruit-based laxatives are well tolerated and associated with improvement in stool consistency and frequency. Increased dietary fiber may cause distention or flatulence, which often diminishes over several days. Soluble fiber supplements (eg, psyllium, methylcellulose) are a convenient, well-tolerated way to increase dietary fiber (Table 15–4). Response to fiber therapy is not immediate and increases in dosage should be made gradually over 7–10 days. Fiber is most likely to benefit patients with normal colonic transit. However, fiber may not benefit patients with symptoms of colonic inertia, defecatory disorders, opioid-induced constipation, or IBS; it may even exacerbate these symptoms. Regular exercise is associated with a decreased risk of constipation. When possible, discontinue medications that may be causing or contributing to constipation. Probiotics are widely promoted in direct advertising to patients for treatment of constipation. Meta-analysis of randomized controlled trials suggests probiotics improve stool frequency and consistency; however, more study is needed.

2. Laxatives—Laxatives may be given on an intermittent or chronic basis for constipation that does not respond to dietary and lifestyle changes (Table 15–4). In a 2020 survey of US adults with constipation symptoms (hard, lumpy, or infrequent stools or straining), 45% were taking fibers supplements or nonprescription laxatives; only 3% were taking prescription laxatives. There is no evidence that long-term use of these agents is harmful.

A. Osmotic laxatives—Treatment usually is initiated with regular (daily) use of an osmotic laxative. Nonabsorbable osmotic agents promote defecation by increased retention of water in the intestinal lumen, leading to softening of the stool and secondary stimulation of colonic peristalsis. Polyethylene glycol 3350 (MiraLax) should be the first-line agent in most situations due to its established efficacy in controlled clinical trials and low incidence of adverse events. MiraLax 17 g once daily has demonstrated superiority to placebo, lactulose, and prucalopride. Nondigestible carbohydrates (sorbitol, lactulose) are efficacious but less preferred because they may cause bloating, cramps, and flatulence. Magnesium-containing laxatives (magnesium hydroxide [milk of magnesia], magnesium oxide, magnesium sulfate) may be suitable for intermittent therapy but should not be given to patients with chronic renal insufficiency. When used in conventional doses, the onset of action of osmotic agents is generally within 24 hours. For more rapid treatment of acute constipation, purgative laxatives may be used, such as magnesium citrate (8–10 oz) or large-volume polyethylene glycol solutions (2–4 L, administered over 2–4 hours). Magnesium citrate may cause hypermagnesemia.

B. Stimulant laxatives—For patients with incomplete response to osmotic agents, stimulant laxatives may be prescribed as needed as a "rescue" agent or on a regular basis (daily or alternate days). These agents stimulate fluid secretion and colonic contraction, resulting in a bowel movement within 6–12 hours after oral ingestion or 15–60 minutes after rectal administration. Oral agents are usually administered once daily at bedtime. Common nonprescription preparations include bisacodyl and senna (Table 15–4).

C. Secretagogues—Several agents stimulate intestinal chloride secretion either through activation of chloride channels (lubiprostone) or guanylcyclase C (linaclotide and plecanatide), resulting in increased intestinal fluid and accelerated colonic transit. In multicenter controlled trials, patients treated with lubiprostone 24 mcg orally twice daily, linaclotide 145 mcg once daily, or plecanatide 3 mg once daily increased the number of bowel movements compared with patients treated with placebo. Because these agents are expensive, they should be reserved for patients who have suboptimal response or side effects with less expensive agents.

D. Serotonin 5-HT-receptor agonist—Prucalopride is a high-affinity 5-HT_4-agonist that is approved in the United States for the treatment of chronic constipation (2 mg once daily). In six clinical trials, 19–38% of patients treated with prucalopride experienced at least three spontaneous bowel movements per week, which was 5–23% more than with placebo. In contrast to prior, less-selective

Table 15–4. Pharmacologic management of constipation.

Agent	Dosage	Onset of Action	Comments
Fiber Laxatives			
Psyllium	1 tbs (3.5 g fiber) once or twice daily	Days	(Metamucil; Perdiem)
Methylcellulose	1 tbs (2 g fiber) once or twice daily	Days	(Citrucel) Less gas, flatulence
Calcium polycarbophil	1 or 2 tablets once or twice daily	12–24 hours	(FiberCon) Does not cause gas; pill form
Guargum	1 tbsp once or twice daily	Days	(Benefiber) Non-gritty, tasteless, less gas
Stool Surfactants			
Docusate sodium	100 mg once or twice daily	12–72 hours	(Colace) Marginal benefit
Mineral oil	15–45 mL once or twice daily	6–8 hours	May cause lipoid pneumonia if aspirated
Osmotic Laxatives			
Magnesium hydroxide	15–30 mL orally once or twice daily	6–24 hours	(Milk of magnesia) May cause hypermagnesemia if CKD
Lactulose or 70% sorbitol	15–60 mL orally once daily to three times daily	6–48 hours	Cramps, bloating, flatulence
Polyethylene glycol (PEG 3350)	17 g in 8 oz liquid once or twice daily	6–24 hours	(MiraLAX); More effective, less bloating than lactulose, sorbitol
Stimulant Laxatives			
Bisacodyl	5–20 mg orally as needed	6–8 hours	May cause cramps; avoid daily use if possible
Bisacodyl suppository	10 mg per rectum as needed	1 hour	
Senna	17.2–34.4 mg orally	8–12 hours	(ExLax; Senekot; SennaS) May cause cramps; avoid daily use if possible
Lubiprostone	24 mcg orally twice daily	12–48 hours	Expensive; may cause nausea. Contraindicated in pregnancy
Linaclotide	72–145 mcg orally once daily		Expensive; contraindicated in pediatric patients
Plecanatide	3–6 mg once daily		Expensive; contraindicated in pediatric patients
Enemas			
Tap water	500 mL per rectum	5–15 minutes	
Sodium phosphate enema	120 mL per rectum	5–15 minutes	Commonly used for acute constipation or to induce movement prior to medical procedures
Mineral oil enema	100–250 mL per rectum	5–15 minutes	To soften and lubricate fecal impaction
Agents used for Acute Purgative or to Clean Bowel Prior to Medical Procedures			
Polyethylene glycol (PEG 3350)	4 L orally administered over 2–4 hours	< 4 hours	(GoLYTELY; CoLYTE; NuLYTE, MoviPrep) Used to cleanse bowel before colonoscopy
Magnesium citrate	10 oz orally	3–6 hours	Lemon-flavored

5-HT_4-agonists (cisapride, tegaserod), which were removed from the market due to adverse cardiovascular events, prucalopride does not have affinity for hERG K^+ channels and does not appear to have any cardiovascular risk.

e. Opioid-receptor antagonists—Long-term use of opioids can cause constipation by increasing tonic, non-propulsive colonic contractions that lead to increased intestinal fluid absorption and dry, hard stools. Methylnaltrexone (450 mg orally once daily), naloxegol (12.5–25 mg orally once daily), and naldemedine (0.2 mg orally once daily) are mu-opioid receptor antagonists that block peripheral opioid receptors (including in the GI tract) without affecting central analgesia. These medications are recommended for the treatment of opioid-induced constipation in patients receiving prolonged opioid therapy who have not had an adequate laxative response with an osmotic agent (usually PEG-3300) and a stimulant laxative (usually bisacodyl or senna) (see Chapter 5). A subcutaneous formulation of methylnaltrexone also is approved for

treatment of patients receiving palliative care for advanced illness who have not responded to conventional laxative regimens.

B. Fecal Impaction

Severe impaction of stool in the rectal vault may result in obstruction to further fecal flow, leading to partial or complete large bowel obstruction. Predisposing factors include medications (eg, opioids), severe psychiatric disease, prolonged bed rest, neurogenic disorders of the colon, and spinal cord disorders. Clinical presentation includes decreased appetite, nausea and vomiting, and abdominal pain and distention. There may be paradoxical "diarrhea" as liquid stool leaks around the impacted feces. Firm feces are palpable on digital examination of the rectal vault. Initial treatment is directed at relieving the impaction with enemas (saline, mineral oil, or diatrizoate) or digital disruption of the impacted fecal material. Long-term care is directed at maintaining soft stools and regular bowel movements (as above).

When to Refer

- Patients with "alarm" symptoms or who are over age 45–50 should be referred for colonoscopy.
- Patients with refractory constipation should be considered for anorectal manometry, balloon expulsion test, and colonic transit study.
- Patients with defecatory disorders may benefit from biofeedback therapy.
- Rarely, surgery (subtotal colectomy) is required for patients with severe colonic inertia.

Bharucha AE et al. Mechanisms, evaluation, and management of chronic constipation. Gastroenterology. 2020;18:1232. [PMID: 31945360]
Oh SJ et al. Chronic constipation in the United States: results from a population-based survey assessing healthcare seeking and use of pharmacotherapy. Am J Gastroenterol. 2020; 115:895. [PMID: 32324606]
Rao S et al. Efficacy and safety of over-the-counter therapies for chronic constipation: an updated systematic review. Am J Gastroenterol. 2021;116:1156. [PMID: 33767108]

GASTROINTESTINAL GAS

1. Belching

Belching (eructation) is the involuntary or voluntary release of gas from the stomach or esophagus. It occurs most frequently after meals, when gastric distention results in transient lower esophageal sphincter (LES) relaxation. Belching is a normal reflex and does not itself denote GI dysfunction. Virtually all stomach gas comes from swallowed air. With each swallow, 2–5 mL of air is ingested, and excessive amounts may result in distention, flatulence, and abdominal pain. This may occur with rapid eating, gum chewing, smoking, and the ingestion of carbonated beverages. Evaluation should be restricted to patients with other complaints such as dysphagia, heartburn, early satiety, or vomiting.

Chronic excessive belching is almost always caused by supragastric belching (voluntary diaphragmatic contraction, followed by upper esophageal relaxation with air inflow to the esophagus) or true air swallowing (aerophagia), both of which are behavioral disorders that are more common in patients with anxiety or psychiatric disorders. These patients may benefit from referral to a behavioral or speech therapist.

Zad M et al. Chronic burping and belching. Curr Treat Options Gastroenterol. 2020;18:33. [PMID: 31974815]

2. Bloating & Flatus

Bloating is a complaint of increased abdominal pressure that may or may not be accompanied by visible distention. Organic causes of acute bloating with distention, vomiting, and/or pain include ascites, GI obstruction (gastric fundoplication, gastric outlet obstruction, small intestine or colon obstruction, and constipation). Complaints of chronic abdominal distention or bloating are common. Some patients swallow excess air (aerophagia, poorly fitting dentures, sleep apnea, and rapid eating) or produce excess gas (excessive FODMAP [fermentable oligosaccharides, disaccharides, monosaccharides, and polyols] ingestion and malabsorption). Others have impaired gas propulsion or expulsion, increased bowel wall tension, enhanced visceral sensitivity, or altered viscerosomatic reflexes leading to abdominal protrusion. Many of these patients have an underlying functional GI disorder such as IBS or functional dyspepsia. Constipation should be treated, and exercise (which accelerates gas propulsion) is recommended. Medications that inhibit GI motility should be avoided (opioids and calcium channel blockers).

Healthy adults pass **flatus** up to 20 times daily and excrete up to 750 mL. Flatus is derived from two sources: swallowed air (primarily nitrogen) and bacterial fermentation of undigested carbohydrate (which produces H_2, CO_2, and methane). A number of short-chain carbohydrates (FODMAPs) are incompletely absorbed in the small intestine and pass into the colon. These include lactose (dairy products); fructose (fruits, corn syrups, and some sweeteners); polyols (stone-fruits, mushrooms, and some sweeteners); and oligosaccharides (legumes, lentils, cruciferous vegetables, garlic, onion, pasta, and whole grains). Abnormal gas production may be caused by increased ingestion of these carbohydrates or, less commonly, by disorders of malabsorption. Foul odor may be caused by garlic, onion, eggplant, mushrooms, and certain herbs and spices.

Determining abnormal from normal amounts of flatus is difficult. Patients who report excess flatus may also complain of bloating, cramping, and altered stool habits (diarrhea or constipation). Patients with a long-standing history of flatulence and no other symptoms or signs of malabsorption disorders can be treated conservatively. Gum chewing and carbonated beverages should be avoided to reduce air swallowing. Lactose intolerance may be assessed by a 2-week trial of a lactose-free diet or by a hydrogen breath test. A list of foods containing FODMAPs should be provided and high FODMAP foods eliminated for 2–4 weeks. If symptoms improve, FODMAP groups may be sequentially introduced to identify triggers. Multiple low-FODMAP

dietary guides are available; however, referral to a knowledgeable dietician may be helpful.

The nonprescription agent Beano (alpha-d-galactosidase enzyme) reduces gas caused by foods containing galacto-oligosaccharides (legumes, chickpeas, lentils) but not other FODMAPs. Activated charcoal may afford relief. Simethicone has no proven benefit.

Many patients report reduced flatus production with use of probiotics, although there has been limited controlled study of these agents for this purpose.

Lacy BE et al. Management of chronic abdominal distention and bloating. Clin Gastroenterol Hepatol. 2021;19:219. [PMID: 32246999]

Scarlata K. Low FODMAP diet: what your patients need to know. Am J Gastroenterol. 2019;114:189. [PMID: 30356177]

DIARRHEA

Diarrhea can range in severity from an acute self-limited episode to a severe, life-threatening illness. To properly evaluate the complaint, the clinician must determine the patient's normal bowel pattern and the nature of the current symptoms.

Approximately 10 L/day of fluid enter the duodenum of which all but 1.5 L/day are absorbed by the small intestine. The colon absorbs most of the remaining fluid, with less than 200 mL/day lost in the stool. Although diarrhea sometimes is defined as a stool weight of more than 200–300 g/24 hours, quantification of stool weight is necessary only in some patients with chronic diarrhea. In most cases, the physician's working definition of diarrhea is increased stool frequency (more than three bowel movements per day) or liquidity of feces.

The causes of diarrhea are myriad. In clinical practice, it is helpful to distinguish acute from chronic diarrhea, as the evaluation and treatment are entirely different (Tables 15–5 and 15–6).

1. Acute Diarrhea

ESSENTIALS OF DIAGNOSIS

- Diarrhea of < 2 weeks' duration is most commonly caused by invasive or noninvasive pathogens and their enterotoxins.

Acute noninflammatory diarrhea

- Watery, nonbloody.
- Usually mild, self-limited.
- Caused by a virus or noninvasive, toxin-producing bacterium.
- Diagnostic evaluation is limited to patients with diarrhea that is severe or persists beyond 7 days.

Acute inflammatory diarrhea

- Blood or pus, fever.
- Usually caused by an invasive or toxin-producing bacterium.

Table 15–5. Causes of acute infectious diarrhea.

Noninflammatory Diarrhea	Inflammatory Diarrhea
Viral Noroviruses, astrovirus, adenovirus, rotavirus, sapovirus, SARS-CoV-2	**Viral** Cytomegalovirus
Protozoal *Giardia lamblia* *Cryptosporidium* *Cyclospora*	**Protozoal** *Entamoeba histolytica*
Bacterial 1. Preformed enterotoxin production *Staphylococcus aureus* *Bacillus cereus* *Clostridium perfringens* 2. Enterotoxin production Enterotoxigenic *Escherichia coli* (ETEC) *Vibrio cholerae, Vibrio vulnificus*	**Bacterial** 1. Cytotoxin production Enterohemorrhagic *E coli* O157:H5 and O157:H7 (EHEC) *Vibrio parahaemolyticus* *Clostridioides difficile* 2. Mucosal invasion *Shigella* *Campylobacter jejuni* *Salmonella* Enteroinvasive *E coli* (EIEC) *Listeria monocytogenes* *Aeromonas* *Yersinia enterocolitica* 3. Infectious proctitis *Chlamydia* *Neisseria gonorrhoeae*

- Diagnostic evaluation requires routine stool bacterial testing (including *E coli* O157:H5 and O157:H7) in all patients and testing as clinically indicated in others for *Clostridioides difficile* and parasites.

Etiology & Clinical Findings

Diarrhea acute in onset and persisting for less than 2 weeks is most commonly caused by infectious agents, bacterial toxins (either preformed or produced in the gut), or medications. Community outbreaks (including norovirus and SARS-CoV-2 in nursing homes, schools, cruise ships) suggest a viral etiology or a common food source. Similar recent illnesses in family members suggest an infectious origin. Among patients with COVID-19 infection, watery diarrhea (usually mild) occurs in one-third and may be the presenting symptom in 3–16%. Ingestion of improperly stored or prepared food implicates "food poisoning" due to bacterial toxins that are either present in the ingested food (preformed) or produced within the GI tract after ingestion. Pregnant women have an increased risk of developing listeriosis. Day care attendance or exposure to unpurified water (camping, swimming) may result in infection with *Giardia* or *Cryptosporidium*. Large *Cyclospora* outbreaks have been traced to contaminated produce. Recent travel abroad suggests "traveler's diarrhea" (see Chapter 30). Antibiotic administration within the preceding several

Table 15–6. Causes of chronic diarrhea.

Osmotic diarrhea
CLUES: Stool volume decreases with fasting; increased stool osmotic gap
1. Medications: antacids, lactulose, sorbitol
2. Disaccharidase deficiency: lactose intolerance
3. Factitious diarrhea: magnesium (antacids, laxatives)

Secretory diarrhea
CLUES: Large volume (> 1 L/day); little change with fasting; normal stool osmotic gap
1. Hormonally mediated: VIPoma, carcinoid, medullary carcinoma of thyroid (calcitonin), Zollinger-Ellison syndrome (gastrin)
2. Factitious diarrhea (laxative abuse); phenolphthalein, senna
3. Villous adenoma
4. Bile salt malabsorption (idiopathic, ileal resection; Crohn ileitis; postcholecystectomy)
5. Medications

Inflammatory conditions
CLUES: Fever, hematochezia, abdominal pain
1. Ulcerative colitis
2. Crohn disease
3. Microscopic colitis
4. Malignancy: lymphoma, adenocarcinoma (with obstruction and pseudodiarrhea)
5. Radiation enteritis

Medications
Common offenders: SSRIs, cholinesterase inhibitors, NSAIDs, PPIs, angiotensin II receptor blockers, metformin, allopurinol

Malabsorption syndromes
CLUES: Weight loss, abnormal laboratory values; fecal fat > 10 g/24 hours
1. Small bowel mucosal disorders: celiac disease, tropical sprue, Whipple disease, eosinophilic gastroenteritis, small bowel resection (short bowel syndrome), Crohn disease
2. Lymphatic obstruction: lymphoma, carcinoid, infectious (tuberculosis, MAI), Kaposi sarcoma, sarcoidosis, retroperitoneal fibrosis
3. Pancreatic disease: chronic pancreatitis, pancreatic carcinoma
4. Bacterial overgrowth: motility disorders (diabetes, vagotomy), systemic sclerosis (scleroderma), fistulas, small intestinal diverticula

Motility disorders
CLUES: Prior abdominal surgery or systemic disease
1. Postsurgical: vagotomy, partial gastrectomy, blind loop with bacterial overgrowth
2. Systemic disorders: systemic sclerosis (scleroderma), diabetes mellitus, hyperthyroidism
3. Irritable bowel syndrome

Chronic infections
1. Parasites: *Giardia lamblia, Entamoeba histolytica, Strongyloides stercoralis, Capillaria philippinensis*
2. AIDS-related: viral: cytomegalovirus; bacterial: *Clostridioides difficile,* MAI; protozoal: microsporidia (*Enterocytozoon bieneusi*), *Cryptosporidium, Cystoisospora belli* (formerly *Isospora belli*)

Factitious
See Osmotic and Secretory diarrhea above

MAI, *Mycobacterium avium-intracellulare.*

weeks increases the likelihood of *C difficile* colitis. Finally, risk factors for HIV infection or sexually transmitted diseases should be determined. (AIDS-associated diarrhea is discussed in Chapter 31; infectious proctitis is discussed later in this chapter under Anorectal Infections.) Persons engaging in anal intercourse or oral-anal sexual activities are at risk for a variety of infections that cause proctitis, including gonorrhea, syphilis, lymphogranuloma venereum, and herpes simplex.

The nature of the diarrhea helps distinguish among different infectious causes (Table 15–5 and Chapter 30, Table 30–3).

A. Noninflammatory Diarrhea

Watery, nonbloody diarrhea associated with periumbilical cramps, bloating, nausea, or vomiting suggests a small bowel source caused by either a virus (rotavirus, norovirus, adenovirus, astrovirus, coronavirus), a toxin-producing bacterium (enterotoxigenic *E coli* [ETEC], *Staphylococcus aureus, Bacillus cereus, Clostridium perfringens*), or another agent (*Giardia*) that disrupts normal absorption and secretory process in the small intestine. Prominent vomiting suggests viral enteritis or food poisoning due to a preformed toxin *(S aureus, B cereus).* Although typically mild, the diarrhea (which originates in the small intestine) can be voluminous and result in dehydration with hypokalemia and metabolic acidosis (eg, cholera). Because tissue invasion does not occur, fecal leukocytes are not present.

B. Inflammatory Diarrhea

The presence of fever and bloody diarrhea (dysentery) indicates colonic tissue damage caused by invasion (shigellosis, salmonellosis, *Campylobacter* or *Yersinia* infection, amebiasis) or a toxin (*C difficile*, Shiga-toxin–producing *E coli* [STEC; also known as enterohemorrhagic *E coli*]). Because these organisms predominantly involve the colon, the diarrhea is small in volume (less than 1 L/day) and associated with left lower quadrant cramps, urgency, and tenesmus. Fecal leukocytes or lactoferrin usually are present in infections with invasive organisms. *E coli* O157:H7 is a Shiga-toxin–producing noninvasive organism most commonly acquired from contaminated meat that has resulted in several outbreaks of an acute, often severe hemorrhagic colitis. A major complication of STEC is hemolytic-uremic syndrome, which develops in 6–22% of cases. In immunocompromised and HIV-infected patients, cytomegalovirus (CMV) can cause intestinal ulceration with watery or bloody diarrhea. *Listeria monocytogenes* has been implicated in several outbreaks of foodborne gastroenteritis, which have been characterized by fever (60–100%), watery diarrhea, and nausea or vomiting.

Infectious dysentery must be distinguished from acute ulcerative colitis, which may also present acutely with fever, abdominal pain, and bloody diarrhea. Immune checkpoint inhibitor therapy for malignancies may cause GI side effects in 8–27% of patients that range from mild diarrhea to severe enterocolitis characterized by abdominal pain and inflammatory diarrhea with mucus, blood, elevated lactoferrin or calprotectin, and colitis at endoscopy. Diarrhea that persists for more than 14 days is not attributable to bacterial pathogens (except for *C difficile*) and should be evaluated as chronic diarrhea.

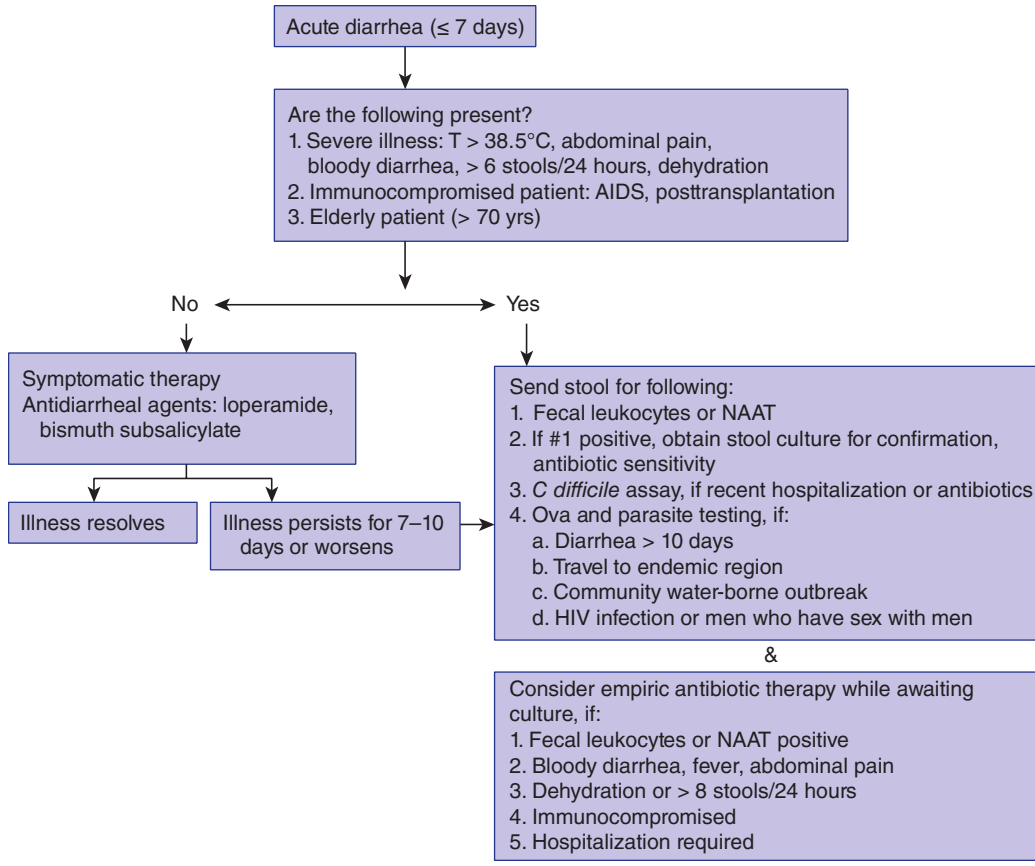
Evaluation

In over 90% of patients with acute noninflammatory diarrhea, the illness is mild and self-limited, responding within 5 days to simple rehydration therapy or antidiarrheal agents. The isolation rate of bacterial pathogens from stool cultures in patients with acute noninflammatory diarrhea is under 3%; therefore, diagnostic investigation is unnecessary except in suspected outbreaks or in patients at high risk for spreading infection to others.

The goal of initial evaluation of acute diarrhea is to distinguish patients with mild disease from those with more serious illness. Prompt medical evaluation is indicated in the following situations (Figure 15–1): (1) signs of inflammatory diarrhea manifested by any of the following: fever (higher than 38.5°C), WBC 15,000/mcL (15×10^9/L) or more, bloody diarrhea, or severe abdominal pain; (2) the passage of six or more unformed stools in 24 hours; (3) profuse watery diarrhea and dehydration; (4) frail older patients or nursing home residents; (5) immunocompromised patients (AIDS, posttransplantation); (6) exposure to antibiotics; (7) hospital-acquired diarrhea (onset following at least 3 days of hospitalization); or (8) systemic illness.

Physical examination pays note to the patient's level of hydration, mental status, and the presence of abdominal tenderness or peritonitis. Peritoneal findings may be present in infection with *C difficile* or STEC. Hospitalization is required in patients with severe dehydration, organ failure, marked abdominal pain, or altered mental status.

Stool should be sent for microbial assessment when patients have dysentery (bloody stools), severe illness, or persistent diarrhea beyond 7 days. Until recently, stool specimens were sent for microscopy (to assess for fecal white cells and protozoa) and bacterial cultures. These traditional methods provided a positive diagnosis in 60–75% of patients with dysenteric diarrhea but required 48–72 hours. Currently, many centers perform microbial assessment using multiplex molecular techniques with nucleic acid amplification (eg, PCR assays) that screen for



▲ **Figure 15–1.** Evaluation of acute diarrhea. NAAT, nucleic acid amplification test.

a panel of pathogens, including viruses, protozoa, and bacteria, within 1–5 hours. If the PCR assay detects a bacterial pathogen, stool culture is recommended for confirmation and antibiotic sensitivity testing. In patients who are hospitalized or who have a history of antibiotic exposure, a stool sample should be tested for *C difficile*. Patients with severe diarrhea or dysentery and a known history of inflammatory bowel disease or prior immune checkpoint inhibitor therapy require expedited evaluation with stool studies and possible sigmoidoscopy or colonoscopy with biopsy to exclude infection (*C difficile*, other bacteria, CMV) prior to therapy with intravenous corticosteroids.

Treatment

A. Diet

Most mild diarrhea will not lead to dehydration provided the patient takes adequate oral fluids containing carbohydrates and electrolytes. Patients find it more comfortable to rest the bowel by avoiding high-fiber foods, fats, milk products, caffeine, and alcohol. Drinking tea and "flat" carbonated beverages and eating soft, easily digested foods (eg, soups, crackers, bananas, applesauce, rice, toast) are encouraged.

B. Rehydration

In more severe diarrhea, dehydration can occur quickly, especially in children and frail older adults. Oral rehydration with fluids containing glucose, Na^+, K^+, Cl^-, and bicarbonate or citrate is preferred when feasible. A convenient mixture is ½ tsp salt (3.5 g), 1 tsp baking soda (2.5 g $NaHCO_3$), 8 tsp sugar (40 g), and 8 oz orange juice (1.5 g KCl), diluted to 1 L with water. Alternatively, oral electrolyte solutions (eg, Pedialyte, Gatorade) are readily available. Fluids should be given at rates of 50–100 mL/kg/24 hours depending on the hydration status. Intravenous fluids (lactated Ringer injection) are preferred in patients with severe dehydration.

C. Antidiarrheal Agents

Antidiarrheal agents may be used safely in patients with mild to moderate diarrheal illnesses to improve patient comfort. Opioid agents help decrease the stool number and liquidity and control fecal urgency. However, they should not be used in patients with bloody diarrhea, high fever, or systemic toxicity and should be discontinued in patients whose diarrhea is worsening despite therapy. With these provisos, such drugs provide excellent symptomatic relief. Loperamide is preferred, in a dosage of 4 mg orally initially, followed by 2 mg after each loose stool (maximum: 8 mg/24 hours). Anticholinergic agents (eg, diphenoxylate with atropine) are contraindicated in acute diarrhea because of the rare precipitation of toxic megacolon.

D. Antibiotic Therapy

1. Empiric treatment—Empiric antibiotic treatment of patients with acute, community-acquired diarrhea generally is not indicated. Even patients with inflammatory diarrhea caused by invasive pathogens usually have symptoms that will resolve within several days without antimicrobials. In centers in which stool microbial testing with rapid molecular assays is not available, empiric treatment may be considered while the stool bacterial culture is incubating, particularly in patients with non–hospital-acquired diarrhea who have moderate to severe fever, tenesmus, or bloody stools and no suspicion of infection with STEC. It should also be considered in patients who are immunocompromised or who have significant dehydration. The oral medications of choice for empiric treatment are the fluoroquinolones (eg, ciprofloxacin 500 mg twice daily, ofloxacin 400 mg, or levofloxacin 500 mg once daily for 1–3 days) or azithromycin (eg, 1 g single dose or 500 mg daily for 3 days). Empiric treatment of noninflammatory traveler's diarrhea is discussed in Chapter 30.

2. Specific antimicrobial treatment—Antibiotics are not recommended in patients with nontyphoid *Salmonella, Campylobacter*, or *Yersinia*, except in severe disease, because they do not hasten recovery or reduce the period of fecal bacterial excretion. STEC infection should not be treated with antibiotics due to an increased risk of hemolytic-uremic syndrome, especially in children. The infectious bacterial diarrheas for which treatment is recommended are shigellosis, cholera, extraintestinal salmonellosis, listeriosis, and *C difficile*. The parasitic infections for which treatment is indicated are amebiasis, giardiasis, cryptosporidiosis, cyclosporiasis, and *Enterocytozoon bienusi* infection. Therapy for traveler's diarrhea, infectious (sexually transmitted) proctitis, and AIDS-related diarrhea is presented in Chapters 30 and 31.

When to Admit

- Severe dehydration for intravenous fluids, especially if vomiting or unable to maintain sufficient oral fluid intake.
- Bloody diarrhea that is severe or worsening in order to distinguish infectious versus noninfectious cause.
- Severe abdominal pain, worrisome for toxic colitis, inflammatory bowel disease, intestinal ischemia, or surgical abdomen.
- Signs of severe infection or sepsis (temperature higher than 39.5°C, leukocytosis, rash).
- Severe or worsening diarrhea in patients who are older than 70 years or immunocompromised.
- Signs of hemolytic-uremic syndrome (AKI, thrombocytopenia, hemolytic anemia).

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2. Chronic Diarrhea

ESSENTIALS OF DIAGNOSIS

- Diarrhea present for > 4 weeks.
- Before embarking on extensive workup, common causes should be excluded, including medications, chronic infections, and IBS.

Etiology

The causes of chronic diarrhea may be grouped into the following major pathophysiologic categories: medications, osmotic diarrheas, secretory conditions, inflammatory conditions, malabsorptive conditions, motility disorders, chronic infections, and systemic disorders (Table 15–6).

A. Medications

Numerous medications can cause diarrhea. All medications should be carefully reviewed, and discontinuation of potential culprits should be considered.

B. Osmotic Diarrheas

As stool leaves the colon, fecal osmolality is equal to the serum osmolality, ie, approximately 290 mOsm/kg. Under normal circumstances, the major osmoles are Na^+, K^+, Cl^-, and HCO_3^-. The stool osmolality may be estimated by multiplying the stool ($Na^+ + K^+$) × 2. The **osmotic gap** is the difference between the *measured* osmolality of the stool (or serum) and the *estimated* stool osmolality and is normally less than 50 mOsm/kg. An increased osmotic gap (greater than 75 mOsm/kg) implies that the diarrhea is caused by ingestion or malabsorption of an osmotically active substance. The most common causes are carbohydrate malabsorption (lactose, fructose, sorbitol), laxative abuse, and malabsorption syndromes. Osmotic diarrheas resolve during fasting. Those caused by malabsorbed carbohydrates are characterized by abdominal distention, bloating, and flatulence due to increased colonic gas production.

Carbohydrate malabsorption is common and should be considered in all patients with chronic, postprandial diarrhea. Patients should be asked about their intake of dairy products (lactose), fruits and artificial sweeteners (fructose and sorbitol), processed foods and soft drinks (high-fructose corn syrup), and alcohol. The diagnosis of carbohydrate malabsorption may be established by an elimination trial for 2–3 weeks or by hydrogen breath tests.

Ingestion of magnesium- or phosphate-containing compounds (laxatives, antacids) should be considered in enigmatic chronic diarrhea. The fat substitute olestra also causes diarrhea and cramps in occasional patients.

C. Secretory Conditions

Increased intestinal secretion or decreased absorption results in a high-volume watery diarrhea with a normal osmotic gap. There is little change in stool output during the fasting state, and dehydration and electrolyte imbalance may develop. Causes include endocrine tumors (stimulating intestinal or pancreatic secretion), bile salt malabsorption (stimulating colonic secretion), and microscopic colitis. Microscopic colitis is a common cause of chronic watery diarrhea in older adults (see Inflammatory Bowel Disease, below).

D. Inflammatory Conditions

Diarrhea is present in most patients with inflammatory bowel disease (ulcerative colitis, Crohn disease). A variety of other symptoms may be present, including abdominal pain, fever, weight loss, and hematochezia.

E. Malabsorptive Conditions

The major causes of malabsorption are small intestinal mucosal diseases, intestinal resections, lymphatic obstruction, small intestinal bacterial overgrowth, and pancreatic insufficiency. Its characteristics are weight loss, osmotic diarrhea, steatorrhea, and nutritional deficiencies. Significant diarrhea in the absence of weight loss is not likely to be due to malabsorption. The physical and laboratory abnormalities related to deficiencies of vitamins or minerals are discussed in Chapter 29.

F. Motility Disorders (Including IBS)

IBS is the most common cause of chronic diarrhea in young adults (see Irritable Bowel Syndrome, below). It should be considered in patients with lower abdominal pain and altered bowel habits who have no other evidence of serious organic disease (weight loss, nocturnal diarrhea, anemia, or GI bleeding). Abnormal intestinal motility secondary to systemic disorders, radiation enteritis, or surgery may result in diarrhea due to rapid transit or to stasis of intestinal contents with bacterial overgrowth, resulting in malabsorption.

G. Chronic Infections

Chronic parasitic infections may cause diarrhea through a number of mechanisms. Pathogens most commonly associated with diarrhea include the protozoans *Giardia, Entamoeba histolytica*, and *Cyclospora* as well as the intestinal nematodes. Strongyloidiasis and capillariasis should be excluded in patients from endemic regions, especially in the presence of eosinophilia. Bacterial infections with *C difficile* and, uncommonly, *Aeromonas* and *Plesiomonas* may cause chronic diarrhea.

Immunocompromised patients are susceptible to infectious organisms that can cause acute or chronic diarrhea (see Chapter 31), including microsporidia, *Cryptosporidium*, CMV, *Cystoisospora belli* (formerly *Isospora belli*), *Cyclospora*, and *Mycobacterium avium* complex.

H. Systemic Conditions

Chronic systemic conditions, such as thyroid disease, diabetes, and collagen vascular disorders, may cause diarrhea through alterations in motility or intestinal absorption.

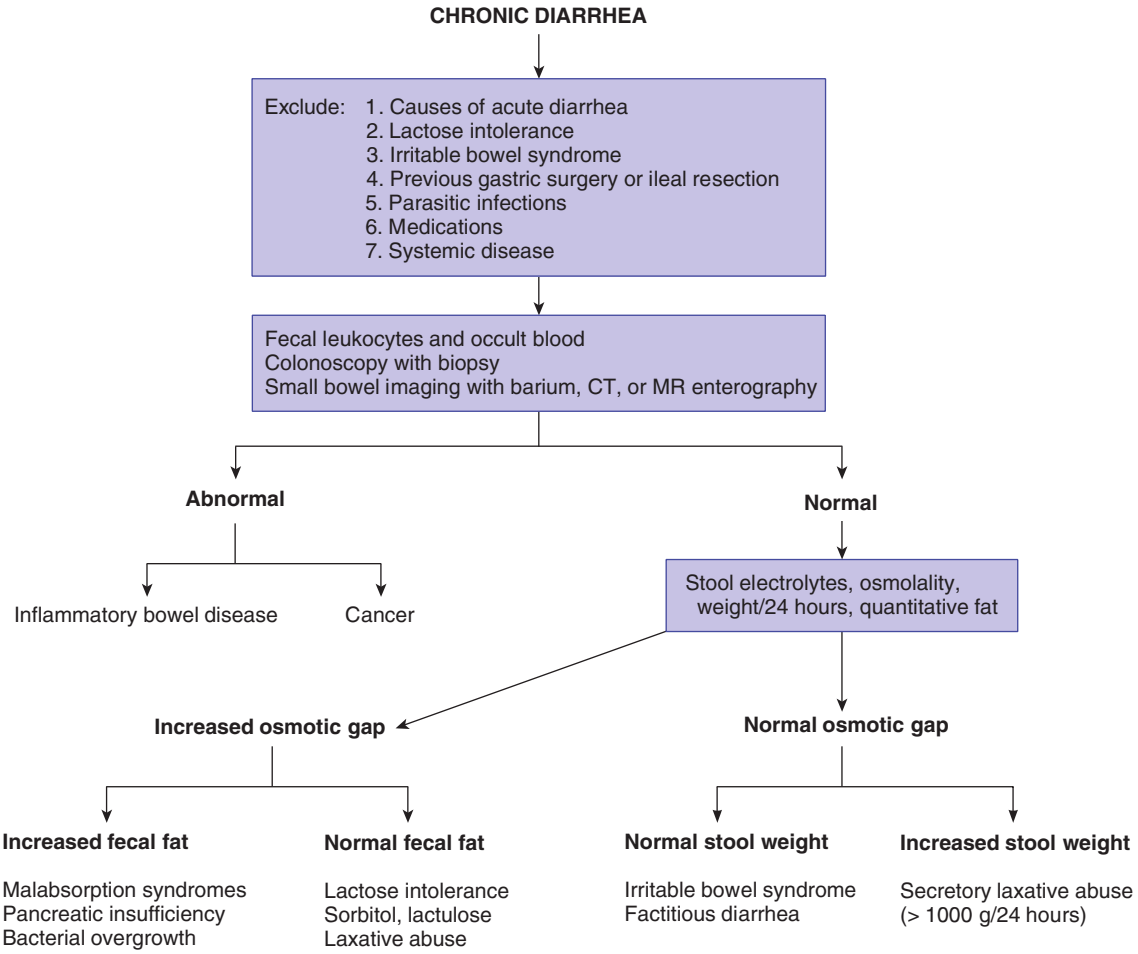
Clinical Findings

The history and physical examination commonly suggest the underlying pathophysiology that guides the subsequent diagnostic workup (Figure 15–2). The clinician should establish whether the diarrhea is continuous or intermittent, whether it has a relationship to meals, and whether it occurs at night or during fasting. The stool appearance may suggest a malabsorption disorder (greasy or malodorous), inflammatory disorder (containing blood or pus), or a secretory process (watery). The presence of abdominal pain suggests IBS or inflammatory bowel disease. Medications, diet, and recent psychosocial stressors should be reviewed. Physical examination should assess for signs of malnutrition, dehydration, and inflammatory bowel disease.

Because chronic diarrhea is caused by so many conditions, the subsequent diagnostic approach is guided by the relative suspicion for the underlying cause, and no specific algorithm can be followed in all patients. Prior to embarking on an extensive evaluation, the most common causes of chronic diarrhea should be considered, including medications, IBS, and lactose intolerance. The presence of nocturnal diarrhea, weight loss, anemia, or positive results on FOBT are inconsistent with these disorders and warrant further evaluation. AIDS-associated diarrhea is discussed in Chapter 31.

A. Initial Diagnostic Tests

1. Routine laboratory tests—CBC, serum electrolytes, liver chemistries, calcium, phosphorus, albumin, TSH, vitamin A and D levels, prothrombin time with INR, ESR, and CRP should be obtained in most patients. Serologic testing for celiac disease with an IgA tissue transglutaminase (IgA anti-tTG) test is recommended in the evaluation of most patients with chronic diarrhea even in the absence of signs of malabsorption. Anemia occurs in malabsorption syndromes (folate, iron, or vitamin B_{12} deficiency) as well as in inflammatory conditions. Hypoalbuminemia is present in malabsorption, protein-losing enteropathies, and inflammatory diseases. Hyponatremia and nonanion gap metabolic acidosis occur in secretory diarrheas. Increased ESR or CRP suggests inflammatory bowel disease. Elevated fasting levels (greater than 48 ng/mL) of the bile acid precursor 7αC4 are strongly predictive of bile acid diarrhea.



▲ **Figure 15–2.** Decision diagram for diagnosis of causes of chronic diarrhea.

2. Routine stool studies—Stool samples should be analyzed for ova and parasites, electrolytes (to calculate osmotic gap), qualitative staining for fat (Sudan stain), occult blood, and either leukocytes or fecal calprotectin or lactoferrin. Parasitic infections (*Giardia*, *E histolytica*, *Cryptosporidia*, and *Cyclospora*) may be diagnosed with stool multiplex PCR assays that test for a panel of pathogens within 1–5 hours, or, where PCR is unavailable, by microscopy with special stains. As discussed previously, an increased osmotic gap suggests an osmotic diarrhea or disorder of malabsorption. A positive fecal fat stain suggests a disorder of malabsorption. In patients with positive fecal fat or suspicion for chronic pancreatitis, a stool sample should be sent for measurement of pancreatic elastase, which is low with pancreatic insufficiency. The presence of fecal leukocytes or elevated calprotectin or lactoferrin may suggest inflammatory bowel disease.

3. Endoscopic examination and mucosal biopsy—Most patients with chronic persistent diarrhea undergo colonoscopy with mucosal biopsy to exclude inflammatory bowel disease (including Crohn disease and ulcerative colitis), microscopic colitis, and colonic neoplasia. Upper endoscopy with small bowel biopsy is performed when a small intestinal malabsorptive disorder is suspected (celiac disease, Whipple disease) from abnormal laboratory studies or a positive fecal fat stain. It may also be done in patients with advanced AIDS to document *Cryptosporidium*, microsporidia, and *M avium-intracellulare* infection.

B. Further Studies

If the cause of diarrhea is still not apparent, further studies may be warranted.

1. 24-hour stool collection quantification of total weight and fat—A stool weight of less than 200–300 g/24 hours excludes diarrhea and suggests a functional disorder such as IBS. A weight greater than 1000–1500 g suggests a significant secretory process, including neuroendocrine tumors. A fecal fat determination in excess of 10 g/24 hours confirms a malabsorptive disorder. Fecal elastase less than 100 mcg/g may be caused by pancreatic insufficiency. (See Celiac Disease and specific tests for malabsorption, below.)

2. Other imaging studies—Calcification on a plain abdominal radiograph confirms a diagnosis of chronic pancreatitis, although abdominal CT and endoscopic ultrasonography are more sensitive for the diagnosis of chronic pancreatitis as well as pancreatic cancer. Small intestinal imaging with CT or MRI enterography is helpful in the diagnosis of Crohn disease, small bowel lymphoma, carcinoid, and jejunal diverticula. Neuroendocrine tumors may be localized using CT, and metastases may be detected using somatostatin receptor PET scanning. Retention of less than 11% at 7 days of intravenous 75Se-homotaurocholate on scintigraphy suggests bile salt malabsorption; however, this test is unavailable in the United States.

3. Laboratory tests—

A. Serologic tests for neuroendocrine tumors—Secretory diarrheas due to neuroendocrine tumors are rare but should be considered in patients with chronic, high-volume watery diarrhea (greater than 1 L/day) with a normal osmotic gap that persists during fasting. Measurements of the secretagogues of various neuroendocrine tumors may be assayed, including serum chromogranin A (pancreatic neuroendocrine tumors), vasoactive intestinal peptide (VIP) (VIPoma), calcitonin (medullary thyroid carcinoma), gastrin (Zollinger-Ellison syndrome), and urinary 5-hydroxyindoleacetic acid (5-HIAA) (carcinoid).

B. Breath test—The diagnosis of small bowel bacterial overgrowth is suggested by a noninvasive breath test (glucose or lactulose); however, a high rate of false-positive test results limits the utility of these tests. A definitive diagnosis of bacterial overgrowth is determined by aspirate of small intestinal contents for quantitative aerobic and anaerobic bacterial culture; however, this procedure is not available at most centers.

Treatment

A number of antidiarrheal agents may be used in certain patients with chronic diarrheal conditions and are listed below. Opioids are safe in most patients with chronic, stable symptoms.

Loperamide: 4 mg orally initially, then 2 mg after each loose stool (maximum: 16 mg/day).

Diphenoxylate with atropine: One tablet orally three or four times daily as needed.

Codeine and **deodorized tincture of opium:** Because of potential habituation, these drugs are avoided except in cases of chronic, intractable diarrhea. Codeine may be given in a dosage of 15–60 mg orally every 4 hours; tincture of opium, 0.3–1.2 mL orally every 6 hours as needed.

Clonidine: Alpha-2-adrenergic agonists inhibit intestinal electrolyte secretion. Clonidine, 0.1–0.3 mg orally twice daily, or a clonidine patch, 0.1–0.2 mg/day, may help in some patients with secretory diarrheas, diabetic diarrhea, or cryptosporidiosis.

Octreotide: This somatostatin analog stimulates intestinal fluid and electrolyte absorption and inhibits intestinal fluid secretion and the release of GI peptides. It is given for secretory diarrheas due to neuroendocrine tumors (VIPomas, carcinoid). Effective doses range from 50 mcg to 250 mcg subcutaneously three times daily.

Bile salt binders: Cholestyramine 2–4 g or colestipol (1–2 g once to three times daily) or colesevelam (625 mg, 1–3 tablets once or twice daily) may be useful in patients with bile salt-induced diarrhea, which may be idiopathic or secondary to intestinal resection or ileal disease.

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GI BLEEDING

1. Acute Upper GI Bleeding

ESSENTIALS OF DIAGNOSIS

- Hematemesis (bright red blood or "coffee grounds").
- Melena in most cases; hematochezia in massive upper GI bleeds.
- Volume status to determine severity of blood loss; hematocrit is a poor early indicator of blood loss.
- Endoscopy diagnostic and may be therapeutic.

General Considerations

There are over 250,000 hospitalizations a year in the United States for acute upper GI bleeding. In the United States, the mortality rate for nonvariceal upper GI bleeding has declined steadily over the past 20 years to 2.1%. Mortality is higher in patients who are older than age 60 years and in patients in whom bleeding develops during hospitalization. Patients seldom die of exsanguination but rather of complications from an underlying disease.

The most common presentation of upper GI bleeding is hematemesis or melena. Hematemesis may be either bright red blood or brown "coffee grounds" material. Melena develops after as little as 50–100 mL of blood loss in the upper GI tract, whereas hematochezia requires a loss of more than 1000 mL. Although hematochezia generally suggests a lower bleeding source (eg, colonic), severe upper GI bleeding may present with hematochezia in 10% of cases.

Upper GI bleeding is self-limited in 80% of patients; urgent medical therapy and endoscopic evaluation are obligatory in the rest. Patients with bleeding more than 48 hours prior to presentation have a low risk of recurrent bleeding.

Etiology

Peptic ulcers account for 40% of major upper GI bleeding with an overall mortality rate of less than 5%. In North America, the incidence of bleeding from ulcers is declining due to eradication of *H pylori* and prophylaxis with PPIs in high-risk patients.

Portal hypertension accounts for 10–20% of upper GI bleeding. Bleeding usually arises from esophageal varices and less commonly gastric or duodenal varices or portal hypertensive gastropathy. Approximately 25% of patients with cirrhosis have medium to large esophageal varices, of whom 30% experience acute variceal bleeding within a 2-year period. Due to improved care, the hospital mortality rate has declined over the past 20 years from 40% to 15%. Nevertheless, a mortality rate of 60–80% is expected at 1–4 years due to recurrent bleeding or other complications of chronic liver disease.

Lacerations of the gastroesophageal junction cause 5–10% of cases of upper GI bleeding. Many patients report a history of heavy alcohol use or retching. Less than 10% have continued or recurrent bleeding.

Vascular anomalies are found throughout the GI tract and may be the source of chronic or acute GI bleeding. They account for 7% of cases of acute upper tract bleeding. The most common are **angioectasias** (angiodysplasias), which are 1–10 mm distorted, aberrant submucosal vessels caused by chronic, intermittent obstruction of submucosal veins. They have a bright red stellate appearance and occur throughout the GI tract but most commonly in the right colon. **Telangiectasias** are small, cherry red lesions caused by dilation of venules that may be part of systemic conditions (hereditary hemorrhagic telangiectasia, CREST syndrome) or occur sporadically. The **Dieulafoy lesion** is an aberrant, large-caliber submucosal artery, most commonly in the proximal stomach that causes recurrent, intermittent bleeding.

Gastric neoplasms cause about 1% of upper GI hemorrhages.

Erosive gastritis is superficial, so it is a relatively unusual cause of severe GI bleeding (less than 5% of cases) and more commonly results in chronic blood loss. Gastric mucosal erosions are due to NSAIDs, alcohol, or severe medical or surgical illness (stress-related mucosal disease).

Severe erosive esophagitis due to chronic gastroesophageal reflux may rarely cause significant upper GI bleeding, especially in patients who are bedbound long-term.

An aortoenteric fistula complicates 2% of abdominal aortic grafts or, rarely, can occur as the initial presentation of a previously untreated aneurysm. Unusual causes of upper GI bleeding include hemobilia (from hepatic tumor, angioma, penetrating trauma), and pancreatic malignancy and pseudoaneurysm (hemosuccus pancreaticus).

Initial Evaluation & Treatment

A. Stabilization

The initial step is assessment of the hemodynamic status. A systolic blood pressure lower than 100 mm Hg identifies a high-risk patient with severe acute bleeding. A heart rate over 100 beats/minute with a systolic blood pressure over 100 mm Hg signifies moderate acute blood loss. A normal systolic blood pressure and heart rate suggest relatively minor hemorrhage. Postural hypotension and tachycardia are useful when present but may be due to causes other than blood loss. Because the hematocrit may take 24–72 hours to equilibrate with the extravascular fluid, it is not a reliable indicator of the severity of acute bleeding.

In patients with significant bleeding, two 18-gauge or larger intravenous lines should be started prior to further diagnostic tests. Blood is sent for CBC, prothrombin time with INR, serum creatinine, liver enzymes, and blood typing and screening (in anticipation of the possible need for transfusion). In patients without hemodynamic compromise or overt active bleeding, aggressive fluid repletion can be delayed until the extent of the bleeding is further clarified. Patients with evidence of hemodynamic compromise are given 0.9% saline or lactated Ringer infusion and cross-matched for 2–4 U of packed RBCs. It is rarely necessary to administer type-specific or O-negative blood.

Central venous pressure monitoring is desirable in some cases, but line placement should not interfere with rapid volume resuscitation.

Placement of a nasogastric tube is not routinely recommended in clinical guidelines but may be helpful in the initial assessment and triage of selected patients with suspected active upper tract bleeding. The aspiration of red blood or "coffee grounds" confirms an upper GI source of bleeding, though up to 18% of patients with confirmed upper tract sources of bleeding have nonbloody aspirates—especially when bleeding originates in the duodenum. Erythromycin (250 mg) administered intravenously 30 minutes prior to upper endoscopy promotes gastric emptying and may improve the quality of endoscopic evaluation when substantial amounts of blood or clot in the stomach is suspected. Efforts to stop or slow bleeding by gastric lavage with large volumes of fluid are of no benefit and expose the patient to an increased risk of aspiration.

B. Blood Replacement

The amount of fluid and blood products required is based on assessment of vital signs, evidence of active bleeding from nasogastric aspirate, and laboratory tests. In patients who are hemodynamically stable, a restrictive policy for RBC transfusion is recommended utilizing a threshold of less than 7 g/dL in most patients but less than 8 g/dL in patients with known CVD. In the absence of continued bleeding, the hemoglobin should rise approximately 1 g/dL for each unit of transfused packed RBCs. Sufficient packed RBCs should be given to maintain a hemoglobin of 7–9 g/dL. In patients with severe GI bleeding, it is desirable to transfuse blood before the hemoglobin reaches 7 g/dL to prevent decreases below that level occurring from hemodilution with fluid resuscitation. Transfusion of blood should not be withheld from patients with massive active bleeding regardless of the hemoglobin value. In actively bleeding patients, platelets are transfused if the platelet count is under 50,000/mcL (50×10^9/L) and considered if there is impaired platelet function due to aspirin or clopidogrel use (regardless of the platelet count). Uremic patients (who also have dysfunctional platelets) with active bleeding are given three doses of desmopressin (DDAVP), 0.3 mcg/kg intravenously, at 12-hour intervals. In patients with active bleeding who have been taking anticoagulation therapy, the benefits of reversal of anticoagulation (reduced bleeding and reduced need for blood products) must be weighed against the risks (thromboembolism, ischemia). In general, endoscopy may be performed safely and effective hemostasis treatment applied if the INR is less than 2.5. In patients taking warfarin, anticoagulation with active bleeding and INR greater than 2.5, either fresh frozen plasma or four factor prothrombin complex (Kcentra®) may be administered. In the face of massive bleeding, administration of four factor prothrombin complex concentrates is preferred (rather than fresh frozen plasma) because it is more rapid and effective at correcting the INR and requires a smaller volume. In patients receiving anticoagulation therapy with the direct thrombin inhibitor (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban, edoxaban), restoration of normal anticoagulation usually requires 24–48 hours (presuming normal kidney and liver function). Therefore, reversal should only be considered in patients with life-threatening bleeding. Idarucizumab (an intravenous monoclonal antibody) is approved for the reversal of dabigatran, and andexanet alfa (a modified factor Xa decoy protein) is approved for the reversal of apixaban and rivaroxaban. For management of coagulation abnormalities in patients with cirrhosis and upper GI bleeding, see Esophageal Varices.

C. Initial Triage

A preliminary assessment of risk based on several clinical factors aids in the resuscitation as well as the rational triage of the patient. Clinical predictors of increased risk of further bleeding and death include liver disease, heart failure, syncope, systolic blood pressure less than 110 mm Hg, pulse greater than 100 beats/minute, bright red blood in the nasogastric aspirate or on rectal examination, and initial hemoglobin less than 13 g/dL (in men) or less than 12 g/dL (in women).

1. High risk—Patients with active bleeding manifested by hematemesis or bright red blood on nasogastric aspirate, shock, persistent hemodynamic derangement despite fluid resuscitation, serious comorbid medical illness, or evidence of advanced liver disease require admission to an ICU. Endoscopy should be performed within 12–24 hours in most patients, but only after adequate hemodynamic resuscitation and management of other active comorbidities (eg, acute coronary syndrome). In a large randomized controlled trial of patients with acute upper GI bleeding deemed at high risk for recurrent bleeding or death, there was no difference in 30-day mortality among patients in whom endoscopy was performed within 6 hours versus within 6–24 hours.

2. Low to moderate risk—All other patients are admitted to an observation unit, medical ward, or step-down unit after appropriate stabilization for further evaluation and treatment. Patients without evidence of active bleeding undergo nonemergent endoscopy, usually within 24 hours.

Subsequent Evaluation & Treatment

Specific treatment of the various causes of upper GI bleeding is discussed elsewhere in this chapter. The following general comments apply to most patients with bleeding.

The clinician's impression of the bleeding source is correct in only 40% of cases. Signs of chronic liver disease implicate bleeding due to portal hypertension, but a different lesion is identified in 25% of patients with cirrhosis. A history of dyspepsia, NSAID use, or peptic ulcer disease suggests peptic ulcer. Acute bleeding preceded by heavy alcohol ingestion or retching suggests a Mallory-Weiss tear, though most patients with Mallory-Weiss tears have neither.

A. Upper Endoscopy

Virtually all patients with upper tract bleeding should undergo upper endoscopy within 24 hours of arriving in

the emergency department. The benefits of endoscopy in this setting are threefold.

1. To identify the source of bleeding—The appropriate acute and long-term medical therapy is determined by the cause of bleeding. Patients with portal hypertension will be treated differently from those with ulcer disease. If surgery or radiologic interventional therapy is required for uncontrolled bleeding, the source of bleeding identified at endoscopy will determine the approach.

2. To determine the risk of rebleeding and guide triage—Patients with a nonbleeding Mallory-Weiss tear, esophagitis, gastritis, and ulcers that have a clean, white base have a very low risk (less than 5%) of rebleeding. Patients with one of these findings who are younger than 60 years, without hemodynamic instability or transfusion requirement, without serious coexisting illness, and who have stable social support may be discharged from the emergency department or medical ward after endoscopy with outpatient follow-up. All others with one of these low-risk lesions should be observed on a medical ward for 24–48 hours. Patients with ulcers that are actively bleeding or have a visible vessel or adherent clot, or who have variceal bleeding usually require at least a 3-day hospitalization with closer initial observation in an ICU or step-down unit.

3. To render endoscopic therapy—Hemostasis can be achieved in actively bleeding lesions with endoscopic modalities such as cautery, injection, or endoclips. About 90% of bleeding or nonbleeding varices can be effectively treated immediately with application of rubber bands to the varices. Similarly, 90% of bleeding ulcers, angiomas, or Mallory-Weiss tears can be controlled with either endoscopic injection of epinephrine, direct cauterization of the vessel by a heater probe or multipolar electrocautery probe, clips, or application of a hemostatic powder spray (TC-325). Certain nonbleeding lesions, such as ulcers with visible blood vessels, and angioectasias are also treated with these therapies. Specific endoscopic therapy of varices, peptic ulcers, and Mallory-Weiss tears is dealt with elsewhere in this chapter.

B. Acute Pharmacologic Therapies

1. Acid inhibitory therapy—Intravenous PPIs (esomeprazole or pantoprazole, 80 mg bolus, followed by 8 mg/hours continuous infusion for 72 hours) reduce the risk of rebleeding in patients with peptic ulcers with high-risk features (active bleeding, visible vessel, or adherent clot) after endoscopic treatment. **Oral PPIs** (omeprazole, esomeprazole, or pantoprazole 40 mg; lansoprazole or dexlansoprazole 30–60 mg) once or twice daily are sufficient for lesions at low-risk for rebleeding (eg, esophagitis, gastritis, clean-based ulcers, and Mallory-Weiss tears).

Administration of continuous intravenous PPI *before* endoscopy results in a decreased number of ulcers with lesions that require endoscopic therapy. It therefore is standard clinical practice at many institutions to administer either an intravenous or a high-dose oral PPI prior to endoscopy in patients with significant upper GI bleeding. Based on the findings during endoscopy, the intravenous PPI may be continued or discontinued.

2. Octreotide—Continuous intravenous infusion of octreotide (100 mcg bolus, followed by 50–100 mcg/hour) reduces splanchnic blood flow and portal blood pressures and is effective in the initial control of bleeding related to portal hypertension. It is administered promptly to all patients with active upper GI bleeding and evidence of liver disease or portal hypertension until the source of bleeding can be determined by endoscopy. In countries where it is available, terlipressin may be preferred to octreotide for the treatment of bleeding related to portal hypertension because of its sustained reduction of portal and variceal pressures and its proven reduction in mortality.

C. Other Treatment

1. Intra-arterial embolization—Angiographic treatment is used in patients with persistent bleeding from ulcers, angiomas, or Mallory-Weiss tears who have failed endoscopic therapy and are poor operative risks. Compared with surgical intervention for recurrent or refractory bleeding, embolization achieves equivalent clinical success rates with lower mortality.

2. Transvenous intrahepatic portosystemic shunts (TIPS)—Placement of a wire stent from the hepatic vein through the liver to the portal vein provides effective decompression of the portal venous system and control of acute variceal bleeding. It is indicated in patients in whom endoscopic modalities have failed to control acute variceal bleeding.

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2. Acute Lower GI Bleeding

ESSENTIALS OF DIAGNOSIS

- Hematochezia usually present.
- Ten percent of cases of hematochezia due to upper GI source.
- Evaluation with colonoscopy in stable patients.
- Massive active bleeding calls for evaluation with CT angiography, followed by upper endoscopy, or angiography.

General Considerations

Lower GI bleeding is defined as that arising below the ligament of Treitz, ie, the small intestine or colon; however, up

to 95% of cases arise from the colon. The severity of lower GI bleeding ranges from mild anorectal bleeding to massive, large-volume hematochezia. Bright red blood that drips into the bowl after a bowel movement or is mixed with solid brown stool signifies mild bleeding, usually from an anorectosigmoid source, and can be evaluated in the outpatient setting. In patients hospitalized with GI bleeding, lower tract bleeding is one-third as common as upper GI hemorrhage and tends to have a more benign course. Patients hospitalized with lower GI tract bleeding are less likely to present with shock or orthostasis (less than 5%) or to require transfusions (less than 40%). Spontaneous cessation of bleeding occurs in over 75% of cases, and hospital mortality is approximately 1%.

Etiology

The cause of these lesions depends on both the age of the patient and the severity of the bleeding. In patients under 50 years of age, the most common causes are infectious colitis, anorectal disease, and inflammatory bowel disease. In older patients, significant hematochezia is most often seen with diverticulosis, angioectasias, malignancy, or ischemia. There is an increased risk of lower GI bleeding in patients taking aspirin, nonaspirin antiplatelet agents, NSAIDs, and anticoagulants.

A. Diverticulosis

Hemorrhage occurs in 3–5% of all patients with diverticulosis and is the most common cause of major lower tract bleeding, accounting for over 50% of cases. Diverticular bleeding usually presents as acute, painless, large-volume maroon or bright red hematochezia in patients over age 50 years. More than 95% of cases require less than 4 units of blood transfusion. Bleeding subsides spontaneously in 80% but may recur in up to 25% of patients.

B. Angioectasias

Angioectasias (angiodysplasias) occur throughout the upper and lower intestinal tracts and cause painless bleeding ranging from melena or hematochezia to occult blood loss. They are responsible for 5% of cases of lower GI bleeding, where they are most often seen in the cecum and ascending colon. They are flat, red lesions (2–10 mm) with ectatic peripheral vessels radiating from a central vessel and are most common in patients over age 70 years and in those with CKD. Bleeding in younger patients more commonly arises from the small intestine.

Ectasias can be identified in up to 6% of persons over age 60 years, so the mere presence of ectasias does not prove that the lesion is the source of bleeding, since active bleeding is seldom seen.

C. Neoplasms

Benign polyps and malignant carcinomas are associated with chronic occult blood loss or intermittent anorectal hematochezia. They may cause up to 7% of acute lower GI hemorrhage.

After endoscopic removal of colonic polyps, important bleeding may occur up to 2 weeks later in 0.1–1% of patients overall but in 3–10% following mucosal resection of large (greater than 2 cm) polyps. In up to one-half of cases, colonoscopy is required to treat postpolypectomy hemorrhage and minimize the need for transfusions.

D. Inflammatory Bowel Disease

Patients with inflammatory bowel disease (especially ulcerative colitis) often have diarrhea with variable amounts of hematochezia. Bleeding varies from occult blood loss to recurrent hematochezia mixed with stool. Symptoms of abdominal pain, tenesmus, and urgency are often present.

E. Anorectal Disease

Anorectal disease (hemorrhoids, fissures) usually results in small amounts of bright red blood noted on the toilet paper, streaking of the stool, or dripping into the toilet bowl; clinically significant blood loss can sometimes occur. Hemorrhoids are the source in 10% of patients admitted with lower bleeding. Rectal ulcers may account for up to 8% of lower bleeding, usually in older adults or debilitated patients with constipation.

F. Ischemic Colitis

This condition is seen commonly in older patients, most of whom have atherosclerotic disease. Most cases occur spontaneously due to transient episodes of nonocclusive ischemia. Ischemic colitis may also occur in 5% of patients after surgery for ileoaortic aneurysm or an AAA. In younger patients, colonic ischemia may develop due to vasculitis, coagulation disorders, estrogen therapy, and long-distance running. Ischemic colitis results in hematochezia or bloody diarrhea associated with mild cramps. In most patients, the bleeding is mild and self-limited.

G. Others

Chronic radiation-induced changes in the rectum may cause anorectal bleeding that develops months to years after pelvic radiation of urologic, gynecologic, or anorectal malignancies. Endoscopy reveals multiple rectal vascular ectasias ("radiation proctopathy"). Acute infectious colitis (see Acute Diarrhea, above) commonly causes bloody diarrhea. Rare causes of lower tract bleeding include vasculitic ischemia, solitary rectal ulcer, NSAID-induced ulcers in the small bowel or right colon, small bowel diverticula, and colonic varices.

Clinical Findings

A. Symptoms and Signs

The color of the stool helps distinguish upper from lower GI bleeding, especially when observed by the clinician. Brown stools mixed or streaked with blood predict a source in the rectosigmoid or anus. Large volumes of bright red blood suggest a colonic source; maroon stools imply a lesion in the right colon or small intestine; and black stools (melena) predict a source proximal to the

ligament of Treitz. Although 10% of patients admitted with self-reported hematochezia have an upper GI source of bleeding (eg, peptic ulcer), this almost always occurs in the setting of massive hemorrhage with hemodynamic instability. Painless large-volume bleeding usually suggests diverticular bleeding. Bloody diarrhea associated with cramping abdominal pain, urgency, or tenesmus is characteristic of inflammatory bowel disease, infectious colitis, or ischemic colitis.

B. Diagnostic Tests

Important considerations in management include exclusion of an upper tract source, anoscopy and sigmoidoscopy, colonoscopy, CT angiography and angiography, and small intestine push enteroscopy or capsule imaging. The studies selected depend on the severity of bleeding at presentation and the presence of hemodynamic instability with suspected ongoing, active bleeding.

1. Anoscopy and sigmoidoscopy—In otherwise healthy patients without anemia under age 45 years with small-volume bleeding, anoscopy and sigmoidoscopy are performed to look for evidence of anorectal disease, inflammatory bowel disease, or infectious colitis. If a lesion is found, no further evaluation is needed immediately unless the bleeding persists or is recurrent. In patients over age 45 years with small-volume hematochezia, the entire colon must be evaluated with colonoscopy to exclude tumor.

2. Colonoscopy—In patients with acute, large-volume bleeding requiring hospitalization, colonoscopy is the preferred initial study in most cases. A meta-analysis of four randomized trials comparing colonoscopy within 24 hours versus elective colonoscopy found that colonoscopy within 24 hours did not reduce length of stay, rebleeding, or mortality. Thus, for patients with stable vital signs and whose lower GI bleeding appears to have stopped (more than 75% of patients), colonoscopy can be performed electively during the hospital stay after appropriate resuscitation and bowel cleansing. For patients who are resuscitated and hemodynamically stable but have signs of continued active bleeding (less than 25% of patients), earlier colonoscopy (within 12–24 hours) can be considered after oral administration of colonic lavage solution (4–8 L of GoLytely, CoLYTE, or NuLyte) over 2–5 hours to clear the bowel of clots. The probable site of bleeding can be identified in 70–85% of patients, and a high-risk lesion can be identified and treated in up to 25%.

3. CT angiography—In patients with massive lower GI bleeding, hemodynamic instability, and suspected active bleeding, urgent radiographic imaging is warranted. Multidetector CT angiography is preferred to technetium-labeled RBC scanning to detect active arterial bleeding and to help localize bleeding to the stomach, upper GI tract, small intestine, right colon, or left colon. In patients with active bleeding demonstrated at CT angiography or in those not effectively treated at colonoscopy, urgent angiography is performed in an attempt to facilitate selective transcatheter embolization therapy.

4. Exclusion of an upper tract source—A nasogastric tube with aspiration should be considered, especially in patients with hemodynamic compromise. Aspiration of red blood or dark brown ("coffee grounds") guaiac-positive material strongly implicates an upper GI source of bleeding. Upper endoscopy should be performed in most patients presenting with hematochezia and hemodynamic instability to exclude an upper GI source, unless prior CT angiography has demonstrated a bleeding site in the lower GI tract.

Treatment

Initial stabilization, blood replacement, and triage are managed in the same manner as described above in Acute Upper GI Bleeding. In patients with ongoing bleeding, consideration should be given to temporary discontinuation of antiplatelet agents for up to 5 days and anticoagulants for 7 days. Compared to persons who do not take long-term low-dose aspirin, the incidence of recurrent lower GI bleeding within 5 years was higher in those who resumed low-dose aspirin postdischarge (18.9% vs 6.9%); however, these patients had a lower risk of serious cardiovascular events (22.8% vs 36.5%) and death (8.2% vs 26.7%).

A. Therapeutic Colonoscopy

High-risk lesions (eg, angioectasia or diverticulum, rectal ulcer with active bleeding, or a visible vessel) may be treated endoscopically with epinephrine injection, cautery (bipolar or heater probe), application of metallic endoclips or bands, or application of a hemostatic powder (TC-325). Radiation-associated vascular ectasias are effectively treated with cautery, preferably with an argon plasma coagulator or with radiofrequency wave ablation or with endorectal instillation of formalin.

B. Intra-arterial Embolization

When a bleeding lesion is identified, angiography with selective embolization achieves immediate hemostasis in more than 95% of patients. Major complications occur in 5% (mainly ischemic colitis) and rebleeding occurs in up to 25%.

C. Surgical Treatment

Emergency surgery is rarely required with acute lower GI bleeding due to the efficacy of colonoscopic and angiographic therapies.

Surgery may be considered in patients with recurrent diverticular hemorrhage depending on the severity of bleeding and the patient's other comorbid conditions.

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3. Suspected Small Bowel Bleeding

Bleeding from the small intestine can be overt or occult. *Overt* small bowel bleeding manifests as melena, maroon stools, or bright red blood per rectum. Up to 5–10% of patients admitted to hospitals with clinically overt GI bleeding do not have a cause identified on upper endoscopy or colonoscopy and may be suspected to have a small bowel source. In up to one-fourth of cases, however, a source of bleeding has been overlooked in the upper or lower tract on prior endoscopic studies. *Occult* small bowel bleeding refers to bleeding that is manifested by recurrent positive FOBTs or FITs or recurrent iron deficiency anemia, or both in the absence of visible blood loss.

Evaluation of Suspected Overt Small Bowel Bleeding

The likely etiology of overt small bowel bleeding depends on the age of the patient. The most common causes of small intestinal bleeding in patients younger than 40 years are neoplasms (stromal tumors, lymphomas, adenocarcinomas, carcinoids), Crohn disease, celiac disease, and Meckel diverticulum. These disorders also occur in patients over age 40; however, angioectasias and NSAID-induced ulcers are far more common.

The evaluation of suspected overt small bowel bleeding depends on the age and overall health status of the patient, associated symptoms, and severity of the bleeding. Before pursuing evaluation of the small intestine, upper endoscopy and colonoscopy are often repeated to ascertain that a lesion in these regions has not been overlooked. Repeat upper endoscopy should be performed with a longer instrument (usually a colonoscope) to evaluate the distal duodenum. If these studies are unrevealing and the patient is hemodynamically stable, capsule endoscopy should be performed to evaluate the small intestine. Further management depends on the capsule endoscopic findings, most commonly, angioectasias (25%), ulcers (10–25%), and neoplasms (1–10%). Multiphasic CT enterography may be considered if capsule endoscopy is unrevealing, since it is more sensitive for the detection of small bowel neoplasms and can exclude hepatic or pancreatic sources of bleeding. Laparotomy is warranted if a small bowel tumor is identified by capsule endoscopy or radiographic studies. Most other lesions identified by capsule imaging can be further evaluated with enteroscopes that use overtubes with balloons to advance the scope through most of the small intestine in a forward and retrograde direction (balloon-assisted enteroscopy). Neoplasms can be biopsied or resected, and angioectasias may be cauterized.

For active, hemodynamically significant acute bleeding, multiphasic CT angiography may be useful to identify and localize active small bowel bleeding and guide subsequent urgent angiography with embolization. A nuclear scan for Meckel diverticulum should be obtained in patients under age 30. With the advent of capsule imaging and advanced endoscopic technologies for evaluating and treating bleeding lesions in the small intestine, intraoperative enteroscopy of the small bowel is seldom required.

4. Occult GI Bleeding

Occult GI bleeding refers to bleeding that is not apparent to the patient. Chronic GI blood loss of less than 100 mL/day may cause no appreciable change in stool appearance. Thus, occult bleeding in an adult is identified by a positive FOBT, FIT, or by iron deficiency anemia in the absence of visible blood loss. FOBT or FIT may be performed in patients with GI symptoms or as a screening test for colorectal neoplasia (see Chapter 39). From 2% to 6% of patients in screening programs have a positive FOBT or FIT.

In the United States, 2% of men and 5% of women have iron deficiency anemia (serum ferritin less than 30–45 mcg/L). In premenopausal women, iron deficiency anemia is most commonly attributable to menstrual and pregnancy-associated iron loss; however, a GI source of chronic blood loss is present in 10%. Occult blood loss may arise from anywhere in the GI tract. Among men and postmenopausal women, a potential GI cause of blood loss can be identified in the colon in 15–30% and in the upper GI tract in 35–55%; a malignancy is present in the lower GI tract in 8.9% and upper tract in 2.0%. Iron deficiency on rare occasions is caused by malabsorption (especially celiac disease) or malnutrition. The most common causes of occult bleeding with iron deficiency are (1) neoplasms; (2) vascular abnormalities (angioectasias); (3) acid-peptic lesions (esophagitis, peptic ulcer disease, erosions in hiatal hernia); (4) infections (nematodes, especially hookworm; tuberculosis); (5) medications (especially NSAIDs or aspirin); and (6) other causes such as inflammatory bowel disease.

Evaluation of Occult Bleeding

Asymptomatic adults with positive FOBTs or FITs that are performed for routine colorectal cancer screening should undergo colonoscopy (see Chapter 39). All symptomatic adults with positive FOBTs or FITs or iron deficiency anemia should undergo evaluation of the lower and upper GI tract with colonoscopy and upper endoscopy, unless the anemia can be definitively ascribed to a nongastrointestinal source (eg, menstruation, blood donation, or recent surgery). Patients with iron deficiency anemia should be evaluated for possible celiac disease with either IgA anti-tTG or duodenal biopsy. After evaluation of the upper and lower GI tract with upper endoscopy and colonoscopy, the origin of occult bleeding remains unexplained in 30–50% of patients. In some of these patients, a source for occult bleeding from a small intestine source is suspected.

For patients with iron deficiency anemia who have no significant findings on upper endoscopy or colonoscopy

and who are without symptoms of small intestinal disease, a 2020 AGA guideline recommends an initial trial of empiric iron therapy. Once daily administration of oral formulations containing 150 mg of elemental iron are commonly recommended, but lower daily doses (60–100 mg) or alternate day dosing may be equally efficacious and better tolerated. A sustained rise in ferritin and hemoglobin with 1–2 months of iron therapy may obviate the need for further studies.

Further investigation of the small intestine is recommended in patients who have anemia that responds poorly to empiric iron supplementation, who have signs of ongoing bleeding (fecal occult blood), or who have worrisome symptoms (abdominal pain, weight loss). Capsule endoscopy is recommended as the initial study in most patients to look for vascular ectasias and to exclude a small intestinal neoplasia or inflammatory bowel disease. If a small intestine source is identified, push enteroscopy, balloon-assisted enteroscopy, abdominal CT, angiography, or laparotomy is pursued, as indicated. When possible, antiplatelet agents (aspirin, NSAIDs, clopidogrel) should be discontinued. Patients with occult bleeding without a bleeding source identified after upper endoscopy, colonoscopy, and capsule endoscopy have a low risk of recurrent bleeding and usually can be managed with close observation.

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DISEASES OF THE PERITONEUM

ASSESSMENT OF THE PATIENT WITH ASCITES

Etiology of Ascites

The term "ascites" denotes the pathologic accumulation of fluid in the peritoneal cavity. Healthy men have little or no intraperitoneal fluid, but women normally may have up to 20 mL depending on the phase of the menstrual cycle. The causes of ascites may be classified into two broad pathophysiologic categories: that which is associated with a normal peritoneum and that which occurs due to a diseased peritoneum (Table 15–7). The most common cause of ascites is portal hypertension secondary to chronic liver disease, which accounts for over 80% of patients with ascites. The management of portal hypertensive ascites is discussed in Chapter 16. The most common causes of nonportal hypertensive ascites include infections (tuberculous peritonitis), intra-abdominal malignancy, inflammatory disorders of the peritoneum, and ductal disruptions (chylous, pancreatic, biliary).

Table 15–7. Causes of ascites.

Normal Peritoneum
Portal hypertension (SAAG ≥ 1.1 g/dL)
1. Hepatic congestion[1]
Heart failure
Constrictive pericarditis
Tricuspid insufficiency
Budd-Chiari syndrome
Veno-occlusive disease
2. Liver disease[2]
Cirrhosis
Alcoholic hepatitis
Fulminant hepatic failure
Massive hepatic metastases
Hepatic fibrosis
Acute fatty liver of pregnancy
3. Portal vein occlusion
4. Miscellaneous
Myxedema
Hypoalbuminemia (SAAG < 1.1 g/dL)
Nephrotic syndrome
Protein-losing enteropathy
Severe malnutrition with anasarca
Miscellaneous conditions (SAAG < 1.1 g/dL)
Chylous ascites
Pancreatic ascites
Bile ascites
Nephrogenic ascites
Urine ascites
Ovarian disease
Diseased peritoneum (SAAG < 1.1 g/dL)[2]
Infections
Bacterial peritonitis
Tuberculous peritonitis
Fungal peritonitis
HIV-associated peritonitis
Malignant conditions
Peritoneal carcinomatosis
Primary mesothelioma
Pseudomyxoma peritonei
Massive hepatic metastases
Hepatocellular carcinoma
Other conditions
Familial Mediterranean fever
Vasculitis
Granulomatous peritonitis
Eosinophilic peritonitis

[1]Hepatic congestion is usually associated with SAAG ≥ 1.1 g/dL and ascitic fluid total protein > 2.5 g/dL.
[2]There may be cases of "mixed ascites" in which portal hypertensive ascites is complicated by a secondary process such as infection. In these cases, the SAAG is ≥ 1.1 g/dL.
SAAG, serum-ascites albumin gradient = serum albumin minus ascitic fluid albumin.

Clinical Findings

A. Symptoms and Signs

The history usually is one of increasing abdominal girth, with the presence of abdominal pain depending on the cause. Because most ascites is secondary to chronic liver disease with portal hypertension, patients should be asked about risk factors for liver disease, especially alcohol consumption, transfusions, tattoos, injection drug use, a history of viral hepatitis or jaundice, and birth in an area endemic for hepatitis. A history of cancer or marked weight loss arouses suspicion of malignant ascites. Fevers may suggest infected peritoneal fluid, including bacterial peritonitis (spontaneous or secondary). Patients with chronic liver disease and ascites are at greatest risk for developing spontaneous bacterial peritonitis. In immigrants, immunocompromised hosts, or severely malnourished alcoholics, tuberculous peritonitis should be considered.

Physical examination should look for signs of portal hypertension and chronic liver disease. Elevated jugular venous pressure may suggest right-sided heart failure or constrictive pericarditis. A large tender liver is characteristic of acute alcoholic hepatitis or Budd-Chiari syndrome (thrombosis of the hepatic veins). Large abdominal wall veins with cephalad flow suggest portal hypertension; inferiorly directed flow implies hepatic vein obstruction. Signs of chronic liver disease include palmar erythema, cutaneous spider angiomas, gynecomastia, muscle wasting and asterixis from hepatic encephalopathy. Anasarca results from heart failure or nephrotic syndrome with hypoalbuminemia. Finally, firm lymph nodes in the left supraclavicular region or umbilicus suggest intra-abdominal malignancy.

The physical examination is relatively insensitive for detecting ascitic fluid. In general, patients must have at least 1500 mL of fluid to be detected reliably by this method. Even the experienced clinician may find it difficult to distinguish between obesity and small-volume ascites. Abdominal ultrasound establishes the presence of fluid.

B. Laboratory Testing

1. Abdominal paracentesis—Abdominal paracentesis is performed as part of the diagnostic evaluation in all patients with new onset of ascites to help determine the cause. It also is recommended for patients admitted to the hospital with cirrhosis and ascites (in whom the prevalence of bacterial peritonitis is 10–20%) and when patients with known ascites deteriorate clinically (with fever, abdominal pain, worsened hepatic encephalopathy or worsened kidney function) to exclude bacterial peritonitis.

a. Inspection—Cloudy ascitic fluid is seen with infection. Milky fluid indicates chylous ascites (due to hypertriglyceridemia). Bloody fluid suggests either a traumatic paracentesis or malignant ascites (in up to 20% of cases).

b. Routine studies—

(1) Cell count—An ascitic WBC count with differential is the most important test. Normal ascitic fluid contains less than 500 leukocytes/mcL (0.5×10^9/L) and less than 250 polymorphonuclear neutrophils (PMNs)/mcL. Any inflammatory condition can cause an elevated ascitic WBC count. A PMN count of greater than 250/mcL (0.25×10^9/L) (neutrocytic ascites) with a PMN percentage of more than 75% of all white cells is highly suggestive of bacterial peritonitis, either spontaneous primary peritonitis or secondary peritonitis (due to an intra-abdominal source of infection, eg, a perforated viscus or appendicitis). An elevated WBC with a predominance of lymphocytes arouses suspicion of tuberculosis or peritoneal carcinomatosis.

(2) Albumin and total protein—The serum-ascites albumin gradient (SAAG) is the best single test for the classification of ascites into portal hypertensive and nonportal hypertensive causes (Table 15–7). Calculated by subtracting the ascitic fluid albumin from the serum albumin, the gradient correlates directly with the portal pressure. An SAAG of 1.1 g/dL or more suggests underlying portal hypertension, while gradients less than 1.1 g/dL implicate nonportal hypertensive causes.

The accuracy of the SAAG exceeds 95% in classifying ascites. It should be recognized, however, that approximately 4% of patients have "mixed ascites," ie, underlying cirrhosis with portal hypertension complicated by a second cause for ascites formation (such as malignancy or tuberculosis). Thus, a high SAAG is indicative of portal hypertension but does not exclude concomitant malignancy.

The ascitic fluid total protein provides some additional clues to the cause. An elevated SAAG and a high protein level (greater than 2.5 g/dL) are seen in most cases of hepatic congestion secondary to cardiac disease or Budd-Chiari syndrome. However, a high ascitic fluid protein is also found in up to 20% of cases of uncomplicated cirrhosis and in two-thirds of patients with malignant ascites.

(3) Culture and Gram stain—The best technique consists of the inoculation of aerobic and anaerobic blood culture bottles with 5–10 mL of ascitic fluid at the patient's bedside, which increases the sensitivity for detecting bacterial peritonitis to over 85% in patients with neutrocytic ascites (greater than 250 PMNs/mcL [0.25×10^9/L]), compared with approximately 50% sensitivity by conventional agar plate or broth cultures.

c. Optional studies—Other ascitic fluid laboratory tests of utility include glucose and LD (helpful in distinguishing spontaneous from secondary bacterial peritonitis); amylase (elevation suggests pancreatic ascites or perforation of the GI tract with leakage of pancreatic secretions); and creatinine (suggests leakage of urine from the bladder or ureters). An ascitic bilirubin concentration that is greater than the serum bilirubin suggests perforation of the biliary tree. Ascitic fluid cytologic examination is ordered if peritoneal carcinomatosis is suspected. Adenosine deaminase may be useful for the diagnosis of tuberculous peritonitis.

C. Imaging

Abdominal ultrasound is useful in confirming presence of ascites and in guiding paracentesis. Both ultrasound and CT imaging are useful in distinguishing between causes of portal and nonportal hypertensive ascites. Doppler ultrasound and CT can detect Budd-Chiari syndrome. In patients with nonportal hypertensive ascites, these studies

are useful in detecting lymphadenopathy and masses in the mesentery, liver, ovaries, and pancreas. Furthermore, they permit directed percutaneous needle biopsies of these lesions. However, ultrasound and CT are not useful for detecting peritoneal carcinomatosis; the role of PET imaging is unclear.

D. Laparoscopy

In evaluating some patients with nonportal hypertensive ascites (low SAAG) or mixed ascites, laparoscopy permits direct visualization and biopsy of the peritoneum, liver, and some intra-abdominal lymph nodes. Cases of suspected peritoneal tuberculosis or suspected malignancy with nondiagnostic CT imaging and ascitic fluid cytology are best evaluated by laparoscopy.

Aithal GP et al. Guidelines on the management of ascites in cirrhosis. Gut. 2021;70:9. [PMID: 33067334]

SPONTANEOUS BACTERIAL PERITONITIS

ESSENTIALS OF DIAGNOSIS

- A history of chronic liver disease and ascites.
- Fever and abdominal pain.
- Peritoneal signs uncommonly encountered on examination.
- Ascitic fluid neutrophil count > 250 WBCs/mcL (0.25×10^9/L).

General Considerations

"Spontaneous" bacterial infection of ascitic fluid occurs in the absence of an apparent intra-abdominal source of infection. It is seen with few exceptions in patients with ascites caused by chronic liver disease. Translocation of enteric bacteria across the gut wall or mesenteric lymphatics leads to seeding of the ascitic fluid, as may bacteremia from other sites. Approximately 20–30% of cirrhotic patients with ascites develop spontaneous peritonitis; however, the incidence is greater than 40% in patients with ascitic fluid total protein less than 1 g/dL, probably due to decreased ascitic fluid opsonic activity.

Virtually all cases of spontaneous bacterial peritonitis are caused by a monomicrobial infection. The most common pathogens are enteric gram-negative bacteria (*E coli, Klebsiella pneumoniae*) or gram-positive bacteria (*Streptococcus pneumoniae*, viridans streptococci, *Enterococcus* species). Anaerobic bacteria are not associated with spontaneous bacterial peritonitis.

Clinical Findings

A. Symptoms and Signs

Spontaneous bacterial peritonitis is symptomatic in 80–90% of patients; fever and abdominal pain are the most common symptoms (present in two-thirds). In many cases, however, the presentation is subtle (eg, a change in mental status due to precipitation or exacerbation of hepatic encephalopathy or a sudden worsening of kidney function).

Physical examination typically demonstrates signs of chronic liver disease with ascites. Abdominal tenderness is present in less than 50% of patients, and its presence suggests other processes. Spontaneous bacterial peritonitis may be present in 10–20% of patients hospitalized with chronic liver disease, sometimes in the absence of any suggestive symptoms or signs.

B. Laboratory Findings

The most important diagnostic test is abdominal paracentesis. Ascitic fluid should be sent for cell count with differential, and blood culture bottles should be inoculated at the bedside; Gram stain and reagent strips are insensitive.

In the proper clinical setting, an ascitic fluid PMN count of greater than 250 cells/mcL (neutrocytic ascites) is presumptive evidence of bacterial peritonitis. The percentage of PMNs is greater than 50–70% of the ascitic fluid WBCs and commonly approximates 100%. Patients with neutrocytic ascites are presumed to be infected and should be started—regardless of symptoms—on antibiotics. Although 10–30% of patients with neutrocytic ascites have negative ascitic bacterial cultures ("culture-negative neutrocytic ascites"), it is presumed that these patients nonetheless have bacterial peritonitis and should be treated empirically. Occasionally, a positive blood culture identifies the organism when ascitic fluid culture is negative.

Differential Diagnosis

Spontaneous bacterial peritonitis must be distinguished from secondary bacterial peritonitis, in which ascitic fluid has become secondarily infected by an intra-abdominal infection. Secondary bacterial infection accounts for 3% of cases of infected ascitic fluid. Causes include appendicitis, diverticulitis, perforated peptic ulcer, and perforated gallbladder. Even in the presence of perforation, clinical symptoms and signs of peritonitis may be lacking owing to the separation of the visceral and parietal peritoneum by the ascitic fluid.

Ascitic fluid total protein, LD, and glucose are useful in distinguishing spontaneous bacterial peritonitis from secondary infection. Up to two-thirds of patients with secondary bacterial peritonitis have at least two of the following: decreased glucose level (less than 50 mg/dL), elevated LD level (greater than serum), and elevated total protein (greater than 1 g/dL). Ascitic neutrophil counts greater than 10,000/mcL (10×10^9/L) also are suspicious; however, most patients with secondary peritonitis have neutrophil counts within the range of spontaneous peritonitis. The presence of multiple organisms on ascitic fluid Gram stain or culture is diagnostic of secondary peritonitis.

If secondary bacterial peritonitis is suspected, abdominal CT imaging of the upper and lower GI tracts should be obtained to look for evidence of an intra-abdominal source of infection. If these studies are negative and secondary peritonitis still is suspected, repeat paracentesis should be

performed after 48 hours of antibiotic therapy to see if the PMN count is decreasing. In secondary bacterial peritonitis, the PMN count is not below the pretreatment value at 48 hours.

Neutrocytic ascites may also be seen in some patients with peritoneal carcinomatosis, pancreatic ascites, or tuberculous ascites. In these circumstances, however, PMNs account for less than 50% of the ascitic WBCs.

Prevention

Up to 70% of patients who survive an episode of spontaneous bacterial peritonitis will have another episode within 1 year. Oral once-daily prophylactic therapy with ciprofloxacin, 500 mg, or trimethoprim-sulfamethoxazole, one double-strength tablet, has been shown to reduce the rate of recurrent infections to less than 20%. Prophylaxis should be considered also in patients who have not had prior bacterial peritonitis but are at increased risk for infection due to low-protein ascites (total ascitic protein less than 1.5 g/dL) with impaired kidney function (serum creatinine 1.2 g/dL or higher) or decompensated cirrhosis (Child-Pugh class C). When used in appropriately selected high-risk patients, prophylactic antibiotics are associated with a lower risk of spontaneous bacterial peritonitis, hepatorenal syndrome, and mortality.

Treatment

Empiric therapy for spontaneous bacterial peritonitis should be initiated with a third-generation cephalosporin (such as cefotaxime, 2 g intravenously every 8–12 hours, or ceftriaxone, 1–2 g intravenously every 24 hours) or a combination beta-lactam/beta-lactamase agent (such as ampicillin/sulbactam, 2 g/1 g intravenously every 6 hours). Because of a high risk of nephrotoxicity in patients with chronic liver disease, aminoglycosides should not be used. Although the optimal duration of therapy is unknown, an empiric course of 5–10 days is recommended, or treatment until the ascites fluid PMN count decreases to less than 250 cells/mcL. For most infections, 5 days is sufficient; however, infections caused by more serious, virulent pathogens (*S aureus*, viridans streptococci, *Pseudomonas*, or Enterobacteriaceae) warrant 10 days of treatment. Patients without significant clinical improvement after 5 days should undergo repeat paracentesis to assess treatment efficacy. If the ascitic neutrophil count has not decreased by 25%, antibiotic coverage should be adjusted (guided by culture and sensitivity results, if available) and secondary causes of peritonitis excluded. If the ascitic PMN count has decreased but remains more than 250 cells/mcL, antibiotics should be continued for an additional 2–3 days before paracentesis is repeated. Patients with suspected secondary bacterial peritonitis should be given broad-spectrum coverage for enteric aerobic and anaerobic flora with a third-generation cephalosporin and metronidazole, pending identification and definitive (usually surgical) treatment of the cause.

Kidney injury develops in up to 40% of patients and is a major cause of death. Intravenous albumin increases effective arterial circulating volume and renal perfusion, decreasing both kidney injury and mortality. Intravenous albumin, 1.5 g/kg on day 1 and 1 g/kg on day 3, should be administered to patients at high risk for hepatorenal failure (ie, patients with baseline creatinine greater than 1 mg/dL, BUN greater than 30 mg/dL, or bilirubin greater than 4 mg/dL). Nonselective beta-blockers increase the risk of hepatorenal syndrome in patients with bacterial peritonitis. They should be discontinued permanently due to their adverse impact on cardiac output, renal perfusion, and long-term survival in advanced cirrhosis.

Prognosis

The mortality rate of spontaneous bacterial peritonitis is 25%, but if the disease is recognized and treated early, it is less than 10%. Since the majority of patients have underlying severe liver disease, many may die of liver failure, hepatorenal syndrome, or bleeding complications of portal hypertension. The most effective treatment for recurrent spontaneous bacterial peritonitis is liver transplantation.

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MALIGNANT ASCITES

Two-thirds of cases of malignant ascites are caused by peritoneal carcinomatosis. The most common causes are primary adenocarcinomas of the ovary, uterus, pancreas, stomach, colon, lung, or breast. The remaining one-third is due to lymphatic obstruction or portal hypertension due to hepatocellular carcinoma or diffuse hepatic metastases. Patients present with nonspecific abdominal discomfort and weight loss associated with increased abdominal girth. Nausea or vomiting may be caused by partial or complete intestinal obstruction. Abdominal CT may be useful to demonstrate the primary malignancy or hepatic metastases but seldom confirms the diagnosis of peritoneal carcinomatosis. In patients with carcinomatosis, paracentesis demonstrates a low serum ascites-albumin gradient (less than 1.1 mg/dL), an increased total protein (greater than 2.5 g/dL), and an elevated WBC (often both neutrophils and mononuclear cells) but with a lymphocyte predominance. Cytology is positive in over 95%, but laparoscopy may be required in patients with negative cytology to confirm the diagnosis and to exclude tuberculous peritonitis, with which it may be confused. Malignant ascites attributable to portal hypertension usually is associated with an increased serum ascites-albumin gradient (greater than 1.1 g/dL), a variable total protein, and negative ascitic cytology. Ascites caused by peritoneal carcinomatosis does not respond to diuretics.

Patients may be treated with periodic large-volume paracentesis for symptomatic relief. Indwelling catheters can be left in place for patients approaching the end of life who require periodic paracentesis for symptomatic relief. Intraperitoneal chemotherapy is sometimes used to shrink the tumor, but the overall prognosis is extremely poor, with only 10% survival at 6 months. Ovarian cancers represent an exception to this rule. With newer treatments consisting of surgical debulking and intraperitoneal chemotherapy, long-term survival from ovarian cancer is possible.

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Bleicher J et al. A palliative approach to management of peritoneal carcinomatosis and malignant ascites. Surg Oncol Clin N Am. 2021;30:475. [PMID: 34053663]
Hodge C et al. Palliation of malignant ascites. J Surg Oncol. 2019;120:67. [PMID: 30903617]

FAMILIAL MEDITERRANEAN FEVER

This is a rare autosomal recessive disorder of unknown pathogenesis that almost exclusively affects people of Mediterranean ancestry, especially Sephardic Jews, Armenians, Turks, and Arabs. Patients lack a protease in serosal fluids that normally inactivates interleukin-8 and the chemotactic complement factor 5A. Symptoms present in most patients before the age of 20 years. It is characterized by episodic bouts of acute peritonitis that may be associated with serositis involving the joints and pleura. Peritoneal attacks are marked by the sudden onset of fever, severe abdominal pain, and abdominal tenderness with guarding or rebound tenderness. If left untreated, attacks resolve within 24–48 hours. Because symptoms resemble those of surgical peritonitis, patients may undergo unnecessary exploratory laparotomy. Colchicine, 0.6 mg orally two or three times daily, has been shown to decrease the frequency and severity of attacks.

Accetturo M. Improvement of *MEFV* gene variants classification to aid treatment decision making in familial Mediterranean fever. Rheumatology. 2020;59:754. [PMID: 31411330]
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MESOTHELIOMA

(See Chapter 39**.)**

DISEASES OF THE ESOPHAGUS

(See Chapter 39 **for Esophageal Cancer.)**

Symptoms

Heartburn, dysphagia, and odynophagia almost always indicate a primary esophageal disorder.

A. Heartburn

Heartburn (pyrosis) is the feeling of substernal burning, often radiating to the neck. Most commonly caused by the reflux of acidic (or, rarely, alkaline) material into the esophagus, heartburn is highly suggestive of GERD.

B. Dysphagia

Dysphagia is defined as difficulty swallowing food or liquid due to the sensation of it sticking in the throat or chest, with a discomfort, or a choking sensation. In a 2020 survey of US adults, 15% of adults reported recent dysphagia that required compensatory maneuvers (avoiding certain foods or cutting into smaller pieces; eating more slowly; drinking liquids). Up to one-half of these adults previously had sought evaluation for their symptoms. Difficulties in swallowing may arise from problems in transferring the food bolus from the oropharynx to the upper esophagus (oropharyngeal dysphagia) or from impaired transport of the bolus through the body of the esophagus (esophageal dysphagia). The history usually suggests the correct diagnosis.

1. Oropharyngeal dysphagia—The oropharyngeal phase of swallowing is a complex process requiring elevation of the tongue, closure of the nasopharynx, relaxation of the upper esophageal sphincter, closure of the airway, and pharyngeal peristalsis. A variety of mechanical and neuromuscular conditions can disrupt this process (Table 15–8). Problems with the oral phase of swallowing cause drooling or spillage of food from the mouth, inability to chew or initiate swallowing, or dry mouth. Pharyngeal dysphagia is characterized by an immediate sense of the bolus catching in the neck, the need to swallow repeatedly to clear food from the pharynx, or coughing or choking during meals. There may be associated dysphonia, dysarthria, or other neurologic symptoms.

Table 15–8. Causes of oropharyngeal dysphagia.

Neurologic disorders
Brainstem cerebrovascular accident, mass lesion
Amyotrophic lateral sclerosis, multiple sclerosis, pseudobulbar palsy, post-polio syndrome, Guillain-Barré syndrome
Parkinson disease, Huntington disease, dementia
Tardive dyskinesia
Muscular and rheumatologic disorders
Myopathies, polymyositis
Oculopharyngeal dystrophy
Sjögren syndrome
Metabolic disorders
Thyrotoxicosis, amyloidosis, Cushing disease, Wilson disease
Medication side effects: anticholinergics, phenothiazines
Infectious diseases
Polio, diphtheria, botulism, Lyme disease, syphilis, mucositis (*Candida*, herpes)
Structural disorders
Zenker diverticulum
Cervical osteophytes, cricopharyngeal bar, proximal esophageal webs
Oropharyngeal tumors
Postsurgical or radiation changes
Pill-induced injury
Motility disorders
Upper esophageal sphincter dysfunction

Table 15–9. Causes of esophageal dysphagia.

Cause	Clues
Mechanical obstruction	**Solid foods worse than liquids**
Schatzki ring	Intermittent dysphagia; not progressive
Peptic stricture	Chronic heartburn; progressive dysphagia
Esophageal cancer	Progressive dysphagia; age over 50 years
Eosinophilic esophagitis	Young adults; small-caliber lumen, proximal stricture, corrugated rings, or white papules
Motility disorder	**Solid and liquid foods**
Achalasia	Progressive dysphagia
Spastic esophageal disorders	Intermittent; not progressive; may have chest pain
Systemic sclerosis (scleroderma)	Chronic heartburn; Raynaud phenomenon
Ineffective esophageal motility	Intermittent; not progressive; commonly associated with GERD

2. Esophageal dysphagia—Esophageal dysphagia may be caused by **mechanical obstructions** of the esophagus or by **motility disorders** (Table 15–9). Patients with **mechanical obstruction** experience dysphagia, primarily for solids. This is recurrent, predictable, and, if the lesion progresses, will worsen as the lumen narrows. Patients with **motility disorders** have dysphagia for both solids and liquids. It is episodic, unpredictable, and can be progressive.

C. Odynophagia

Odynophagia is sharp substernal pain on swallowing that may limit oral intake. It usually reflects severe erosive disease. It is most commonly associated with infectious esophagitis due to *Candida*, herpesviruses, or CMV, especially in immunocompromised patients. It may also be caused by corrosive injury due to caustic ingestions and by pill-induced ulcers.

Diagnostic Studies

A. Upper Endoscopy

Endoscopy is the study of choice for evaluating persistent heartburn, dysphagia, odynophagia, and structural abnormalities detected on barium esophagography. In addition to direct visualization, it allows biopsy of mucosal abnormalities and of normal mucosa (to evaluate for eosinophilic esophagitis) as well as dilation of strictures.

B. Videoesophagography

Oropharyngeal dysphagia is best evaluated with rapid-sequence videoesophagography.

C. Barium Esophagography

Patients with esophageal dysphagia often are evaluated first with a barium esophagography to differentiate between mechanical lesions and motility disorders, providing important information about the latter in particular. In patients in whom there is a high suspicion of a mechanical lesion, many clinicians will proceed first to endoscopic evaluation because it better identifies mucosal lesions (eg, erosions) and permits mucosal biopsy and dilation. However, barium study is more sensitive for detecting subtle esophageal narrowing due to rings, achalasia, and proximal esophageal lesions.

D. Esophageal Manometry

Esophageal motility may be best assessed using high-resolution manometry with multiple, closely spaced sensors. Manometry is indicated (1) to determine the location of the LES to allow precise placement of a conventional electrode pH probe; (2) to establish the etiology of dysphagia in patients in whom a mechanical obstruction cannot be found, especially if a diagnosis of achalasia is suspected by endoscopy or barium study; and (3) for the preoperative assessment of patients being considered for antireflux surgery to exclude an alternative diagnosis (eg, achalasia) or possibly to assess peristaltic function in the esophageal body.

E. Esophageal pH Recording and Impedance Testing

The pH within the esophageal lumen may be monitored continuously for 24–48 hours. There are two kinds of systems in use: catheter-based and wireless. Catheter-based systems use a long transnasal catheter that is connected directly to the recording device. With wireless systems, a capsule is attached directly to the esophageal mucosa under endoscopic visualization and data are transmitted by radiotelemetry to the recording device. The recording provides information about the amount of esophageal acid reflux and the temporal correlations between symptoms and reflux.

Esophageal pH monitoring devices provide information about the amount of esophageal acid reflux but not nonacid reflux. Techniques using combined pH and multichannel intraluminal impedance allow assessment of acid and nonacid liquid reflux. They may be useful in evaluation of patients with atypical reflux symptoms or persistent symptoms despite therapy with PPIs to diagnose hypersensitivity, functional symptoms, and symptoms caused by nonacid reflux.

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GASTROESOPHAGEAL REFLUX DISEASE

ESSENTIALS OF DIAGNOSIS

- Heartburn; may be exacerbated by meals, bending, or recumbency.
- Typical uncomplicated cases do not require diagnostic studies.
- Endoscopy demonstrates abnormalities in one-third of patients.

General Considerations

GERD is a condition that develops when the reflux of stomach contents causes troublesome symptoms or complications. In a 2020 survey of US adults, 31% reported GERD symptoms within the prior week. The two most common symptoms are heartburn and regurgitation. However, other symptoms of GERD include dyspepsia, dysphagia, belching, chest pain, cough, and hoarseness. Although most patients have mild disease, esophageal mucosal damage (reflux esophagitis) develops in up to one-third and more serious complications develop in a few others. Several factors may contribute to GERD.

A. Dysfunction of the Gastroesophageal Junction

The antireflux barrier at the gastroesophageal junction depends on LES pressure, the intra-abdominal location of the sphincter (resulting in a "flap valve" caused by angulation of the esophageal-gastric junction), and the extrinsic compression of the sphincter by the crural diaphragm. In most patients with GERD, baseline LES pressures are normal (10–35 mm Hg). Most reflux episodes occur during transient relaxations of the LES that are triggered by gastric distention by a vagovagal reflex. A subset of patients with GERD have an incompetent (less than 10 mm Hg) LES that results in increased acid reflux, especially when supine or when intra-abdominal pressures are increased by lifting or bending. A hypotensive sphincter is present in up to 50% of patients with severe erosive GERD.

Hiatal hernias are found in one-fourth of patients with nonerosive GERD, three-fourths of patients with severe erosive esophagitis, and over 90% of patients with Barrett esophagus. They are caused by movement of the LES above the diaphragm, resulting in dysfunction of the gastroesophageal junction reflux barrier. Hiatal hernias are common and may cause no symptoms; however, in patients with gastroesophageal reflux, they are associated with higher amounts of acid reflux and delayed esophageal acid clearance, leading to more severe esophagitis and Barrett esophagus. Increased reflux episodes occur during normal swallowing-induced relaxation, transient LES relaxations, and straining due to reflux of acid from the hiatal hernia sac into the esophagus.

Truncal obesity may contribute to GERD, presumably due to an increased intra-abdominal pressure, which contributes to dysfunction of the gastroesophageal junction and increased likelihood of hiatal hernia.

B. Irritant Effects of Refluxate

Esophageal mucosal damage is related to the potency of the refluxate and the amount of time it is in contact with the mucosa. Acidic gastric fluid (pH less than 4.0) is extremely caustic to the esophageal mucosa and is the major injurious agent in the majority of cases. In some patients, reflux of bile or alkaline pancreatic secretions may be contributory.

C. Abnormal Esophageal Clearance

Acid refluxate normally is cleared and neutralized by esophageal peristalsis and salivary bicarbonate. Patients with severe GERD may have diminished clearance due to hypotensive peristaltic contractions (less than 30 mm Hg) or intermittent failed peristalsis after swallowing. Certain medical conditions such as systemic sclerosis (scleroderma) are associated with diminished peristalsis. Sjögren syndrome, anticholinergic medications, and oral radiation therapy may exacerbate GERD due to impaired salivation.

D. Delayed Gastric Emptying

Impaired gastric emptying due to gastroparesis or partial gastric outlet obstruction potentiates GERD.

Clinical Findings

A. Symptoms and Signs

The typical symptom is heartburn. This most often occurs 30–60 minutes after meals and upon reclining. Patients often report relief from taking antacids or baking soda. When this symptom is dominant, the diagnosis is established with a high degree of reliability. Many patients, however, have less specific dyspeptic symptoms with or without heartburn. Overall, a clinical diagnosis of gastroesophageal reflux has a sensitivity and specificity of only 65%. Severity is not correlated with the degree of tissue damage. In fact, some patients with severe esophagitis are only mildly symptomatic. Patients may complain of regurgitation—the spontaneous reflux of sour or bitter gastric contents into the mouth. Dysphagia occurs in one-third of patients and may be due to erosive esophagitis, abnormal esophageal peristalsis, or the development of an esophageal stricture.

"Atypical" or "extraesophageal" manifestations of gastroesophageal disease may occur, including asthma, chronic cough, chronic laryngitis, sore throat, noncardiac chest pain, and sleep disturbances. In the absence of heartburn or regurgitation, atypical symptoms are unlikely to be related to gastroesophageal reflux.

Physical examination and laboratory data are normal in uncomplicated disease.

B. Special Examinations

Initial diagnostic studies are not warranted for patients with typical GERD symptoms suggesting uncomplicated reflux disease. Patients with typical symptoms of heartburn

and regurgitation should be treated empirically with a twice-daily H_2-receptor antagonist or a once-daily PPI for 4–8 weeks. Further investigation is required in patients with symptoms that persist despite empiric acid inhibitory therapy to identify complications of reflux disease and to diagnose other conditions, particularly in patients with "alarm features" (troublesome dysphagia, odynophagia, weight loss, iron deficiency anemia).

1. Upper endoscopy—Upper endoscopy is excellent for documenting the type and extent of tissue damage in gastroesophageal reflux; for detecting other gastroesophageal lesions that may mimic GERD; and for detecting GERD complications, including esophageal stricture, Barrett metaplasia, and esophageal adenocarcinoma. In the absence of prior antisecretory therapy, up to one-third of patients with GERD have visible mucosal damage (known as reflux esophagitis), characterized by single or multiple erosions or ulcers in the distal esophagus at the squamocolumnar junction. In patients treated with a PPI prior to endoscopy, preexisting reflux esophagitis may be partially or completely healed. The Los Angeles (LA) classification grades reflux esophagitis on a scale of A (one or more isolated mucosal breaks 5 mm or less that do not extend between the tops of two mucosal folds) to D (one or more mucosal breaks that involve at least 75% of the esophageal circumference).

2. Barium esophagography—This study should not be performed to diagnose GERD. In patients with severe dysphagia, it is sometimes obtained prior to endoscopy to identify a stricture.

3. Esophageal pH or combined esophageal pH-impedance testing—Esophageal pH monitoring measures the amount of esophageal acid reflux, whereas combined pH-impedance testing measures both acidic and nonacidic reflux. Both tests may also be useful to establish whether there is a temporal relationship between reflux events and symptoms. They are the most accurate studies for documenting gastroesophageal reflux but are unnecessary in most patients who have typical symptoms and satisfactory response to empiric antisecretory therapy. They are indicated in patients with typical symptoms who have unsatisfactory response to empiric therapy, patients with atypical or extraesophageal symptoms, and patients who are being considered for antireflux surgery.

Differential Diagnosis

Symptoms of GERD may be similar to those of other diseases such as angina pectoris, eosinophilic esophagitis, esophageal motility disorders, dyspepsia, peptic ulcer, or functional disorders. Reflux erosive esophagitis may be confused with pill-induced damage, eosinophilic esophagitis, or infections (CMV, herpes, *Candida*).

Complications

A. Barrett Esophagus

This is a condition in which the squamous epithelium of the esophagus is replaced by metaplastic columnar epithelium containing goblet and columnar cells (specialized intestinal metaplasia). Present in 1.5% of the general population and 7–10% of patients with chronic reflux, Barrett esophagus is believed to arise from chronic reflux-induced injury to the esophageal squamous epithelium; however, it is also increased in patients with truncal obesity independent of GERD. Barrett esophagus is suspected at endoscopy from the presence of orange, gastric type epithelium that extends upward more than 1 cm from the gastroesophageal junction into the distal tubular esophagus in a tongue-like or circumferential fashion. Biopsies obtained at endoscopy confirm the diagnosis. Three types of columnar epithelium may be identified: gastric cardiac, gastric fundic, and specialized intestinal metaplasia. There is agreement that the latter carries an increased risk of dysplasia; however, some authorities believe that gastric cardiac mucosa also raises risk.

Barrett esophagus should be treated with long-term PPIs once or twice daily to control reflux symptoms. Although these medications do not appear to cause regression of Barrett esophagus, they may reduce the risk of cancer. Paradoxically, one-third of patients report minimal or no symptoms of GERD, suggesting decreased acid sensitivity of Barrett epithelium. Indeed, over 90% of individuals with Barrett esophagus in the general population do not seek medical attention.

The most serious complication of Barrett esophagus is esophageal adenocarcinoma. It is believed that most adenocarcinomas of the esophagus and many such tumors of the gastric cardia arise from dysplastic epithelium in Barrett esophagus. The incidence of adenocarcinoma in patients with Barrett esophagus is estimated at 0.2–0.5% per year. Although this still is an 11-fold increased risk compared with patients without Barrett esophagus, adenocarcinoma of the esophagus remains a relatively uncommon malignancy in the United States (9000 cases/year). Given the large number of adults with chronic GERD relative to the small number in whom adenocarcinoma develops and the costs and risks of upper endoscopy, a 2019 clinical guideline recommended against endoscopic screening for Barrett esophagus in adults with GERD except in those with one or more risk factors for adenocarcinoma (aged older than 50 years, truncal obesity, current or prior history of smoking, or male gender) or in adults with a family history of Barrett esophagus or esophageal adenocarcinoma.

In patients known to have nondysplastic Barrett esophagus, surveillance endoscopy every 3–5 years is recommended to look for low- or high-grade dysplasia or adenocarcinoma. During endoscopy, biopsies are obtained from nodular or irregular mucosa (which have an increased risk of high-grade dysplasia or cancer) as well as randomly from the esophagus every 1–2 cm. In a 2021 population-based study, initial surveillance endoscopy detected low-grade dysplasia in 10.6%, high-grade dysplasia in 3.1%, and esophageal cancer in 1.8%. In patients with nondysplastic Barrett esophagus, the risk of progression to high-grade dysplasia or cancer is related to the length of Barrett epithelium. This risk is 0.29%/year for those with columnar epithelium lengths of 1–3 cm (short-segment) and 0.91%/year in those with lengths greater than 3 cm (long-segment).

The finding of dysplasia should be confirmed by a second, expert pathologist. The detection of dysplasia is increased with use of the WATS (wide-area trans-epithelial sampling) technique in which a brush is deployed through the endoscope to obtain deep epithelial samples that are analyzed by a central laboratory computer.

Endoscopic therapy now is the standard of care for patients who have Barrett esophagus with dysplasia (low-grade, high-grade) or well-differentiated mucosal adenocarcinoma (Tis or T1a). Therapy should be performed by endoscopists with expertise in advanced resection and ablation techniques. All nodules should be removed with mucosal snare resection or dissection techniques to assess for the presence and depth of cancer. Following resection, ablation of any remaining Barrett mucosa—including flat (nonnodular) high-grade dysplasia—is performed with radiofrequency wave electrocautery or cryotherapy. Current guidelines also recommend that patients with flat *low-grade* dysplasia (confirmed by a second expert pathologist) also be considered for ablation, reserving annual endoscopic surveillance to patients with increased comorbidities and reduced life-expectancy. The efficacy of endoscopic ablation therapies in patients with Barrett dysplasia is supported by several studies. When high-dose PPIs are administered to normalize intraesophageal pH, radiofrequency wave ablation electrocautery eradication of Barrett columnar epithelium is followed by complete healing with normal squamous epithelium in greater than 78% of patients and elimination of dysplasia in 91%.

Endoscopic ablation techniques have a risk of complications (bleeding, perforation, strictures). Therefore, endoscopic eradication therapy currently is not recommended for patients with nondysplastic Barrett esophagus for whom the risk of developing esophageal cancer is low and treatment does not appear to be cost-effective.

B. Peptic Stricture

Stricture formation occurs in about 5% of patients with esophagitis. It is manifested by the gradual development of solid food dysphagia progressive over months to years. Most strictures are located at the gastroesophageal junction. Endoscopy with biopsy is mandatory in all cases to differentiate peptic stricture from stricture by esophageal carcinoma. Active erosive esophagitis is often present. Up to 90% of symptomatic patients are effectively treated by dilation with graduated polyvinyl catheters passed over a wire placed at the time of endoscopy or fluoroscopically, or by balloons passed fluoroscopically or through an endoscope. Dilation is continued over one to several sessions. A luminal diameter of 15–18 mm is usually sufficient to relieve dysphagia. Long-term therapy with a PPI is required to decrease the likelihood of stricture recurrence.

Treatment

A. Medical Treatment

The goal of treatment is to provide symptomatic relief, to heal esophagitis (if present), and to prevent complications. In the majority of patients with uncomplicated disease, empiric treatment is initiated based on a compatible history without the need for further confirmatory studies. Patients not responding and those with suspected complications undergo further evaluation with upper endoscopy or esophageal manometry and pH recording.

1. Mild, intermittent symptoms—Patients with mild or intermittent symptoms that do not impact adversely on quality of life may benefit from lifestyle modifications with medical interventions taken as needed. Patients may find that eating smaller meals and elimination of acidic foods (citrus, tomatoes, coffee, spicy foods), foods that precipitate reflux (fatty foods, chocolate, peppermint, alcohol), and cigarettes may reduce symptoms. Weight loss should be recommended for patients who are overweight or have had recent weight gain. All patients should be advised to avoid lying down within 3 hours after meals (the period of greatest reflux). Patients with nocturnal symptoms should also elevate the head of the bed on 6-inch blocks or a foam wedge to reduce reflux and enhance esophageal clearance.

Patients with infrequent heartburn (less than once weekly) may be treated on demand with antacids or oral H_2-receptor antagonists. Antacids provide rapid relief of heartburn; however, their duration of action is less than 2 hours. Many are available over the counter. Those containing magnesium should not be used for patients with kidney disease, and patients with acute or chronic kidney disease should be cautioned appropriately.

The oral H_2-receptor antagonists come in a variety of strengths: cimetidine 200 mg; famotidine 10 mg and 20 mg; and nizatidine 75 mg and 150 mg. Most of these drug strengths are now available over the counter without need for a prescription. When taken for active heartburn, these agents have a delay in onset of at least 30 minutes. However, once these agents take effect, they provide heartburn relief for up to 8 hours.

2. Troublesome symptoms—

A. Initial therapy—Patients with troublesome reflux symptoms and patients with known complications of GERD (erosive esophagitis, Barrett esophagus, stricture) should be treated with a once-daily oral PPI (omeprazole or rabeprazole, 20 mg; omeprazole, 40 mg with sodium bicarbonate; lansoprazole, 30 mg; dexlansoprazole, 60 mg; esomeprazole or pantoprazole, 40 mg) taken 30 minutes before breakfast for 4–8 weeks. Because there appears to be little difference between these agents in efficacy or side effect profiles, the choice of agent is determined by cost. Oral omeprazole, 20 mg, and lansoprazole, 15 mg, are available as over-the-counter formulations. Once-daily PPIs achieve adequate control of heartburn in 70–80% of patients, complete heartburn resolution in over 50%, and healing of erosive esophagitis (when present) in 75–85%. In contrast, PPIs are less effective in reducing bothersome regurgitation. Because of their superior efficacy and ease of use, PPIs are preferred to H_2-receptor antagonists for the initial treatment of acute and chronic GERD.

B. Long-term therapy—In those who achieve good symptomatic relief with a course of empiric once-daily PPI, therapy may be discontinued after 8–12 weeks. Most patients

(over 80%) will experience relapse of GERD symptoms, usually within 3 months. Patients whose symptoms relapse may be treated with either continuous PPI therapy, intermittent 2- to 4-week courses, or "on demand" therapy (ie, drug taken until symptoms abate) depending on symptom frequency and patient preference. Alternatively, twice-daily H_2-receptor antagonists may be used to control symptoms in patients without erosive esophagitis. Patients who require twice-daily PPI therapy for initial symptom control and patients with complications of GERD, including severe erosive esophagitis, Barrett esophagus, or peptic stricture, should be maintained on long-term therapy with a once- or twice-daily PPI titrated to the lowest effective dose to achieve satisfactory symptom control.

PPIs are considered to be extremely safe. Although a number of safety concerns have been raised in retrospective observational studies, it is difficult to determine whether the modest associations identified are due to a causal relationship. Long-term use of PPIs likely does have a small increased risk of infectious gastroenteritis (including *C difficile*), small intestinal bacterial overgrowth, and micronutrient deficiencies (iron, vitamin B_{12}, magnesium). A large prospective study of over 17,000 patients taking PPIs for a median of 3 years did not find an increased risk of other previously reported adverse events, including pneumonia, bone fractures, kidney disease (due to interstitial nephritis), dementia, or MI. Long-term PPI therapy should be prescribed to patients with appropriate indications and at the lowest effective dose.

3. Unresponsive disease—Up to one-third of patients report inadequate relief of heartburn or regurgitation with once-daily PPI therapy. Approximately 25% respond to an increase in PPI therapy to twice daily (30–45 minutes before breakfast and dinner). Patients unresponsive to twice-daily therapy should undergo endoscopy for detection of severe, inadequately treated reflux esophagitis and for other gastroesophageal conditions (including eosinophilic esophagitis and achalasia) that may mimic GERD. Truly refractory esophagitis may be caused by medical noncompliance, resistance to PPIs, gastrinoma with gastric acid hypersecretion (Zollinger-Ellison syndrome), or pill-induced esophagitis. Patients without endoscopically visible esophagitis should undergo ambulatory esophageal pH monitoring with impedance monitoring to determine whether the symptoms are correlated with reflux (both acid and nonacid reflux) episodes. The study generally is performed on twice-daily PPI therapy to determine the number of reflux episodes (acid and nonacid) and symptom association with reflux episodes. Refractory GERD is diagnosed in patients with confirmed reflux (increased acid reflux or significant correlation of symptoms with acid or nonacid reflux episodes) despite PPI therapy. These patients may be candidates for surgical or endoscopic therapy. Approximately 30% of patients with unresponsive symptoms do not have increased reflux or a significant symptom correlation with reflux episodes and are diagnosed with "functional heartburn," a functional disorder. Treatment with a low-dose tricyclic antidepressant (eg, imipramine or nortriptyline 25 mg orally at bedtime) may be beneficial.

4. Extraesophageal reflux manifestations—Establishing a causal relationship between gastroesophageal reflux and extraesophageal symptoms (eg, asthma, hoarseness, cough, sleep disturbances) is difficult. Gastroesophageal reflux seldom is the sole cause of extraesophageal disorders but may be a contributory factor. Although ambulatory esophageal pH testing can document the presence of increased acid esophageal reflux, it does not prove a causative connection. Current guidelines recommend that a trial of a twice-daily PPI be administered for 2–3 months in patients with suspected extraesophageal GERD syndromes who also have typical GERD symptoms. Improvement of extraesophageal symptoms suggests but does not prove that acid reflux is the causative factor. Esophageal impedance-pH testing may be performed in patients whose extraesophageal symptoms persist after 3 months of PPI therapy and may be considered before PPI therapy in patients without typical GERD symptoms in whom other causes of extraesophageal symptoms have been excluded.

B. Surgical Treatment

Surgical fundoplication affords good to excellent relief of symptoms and healing of esophagitis in over 85% of properly selected patients and can be performed laparoscopically with low complication rates in most instances. Although patient satisfaction is high, typical reflux symptoms recur in 10–30% of patients. Furthermore, new symptoms of dysphagia, bloating, increased flatulence, dyspepsia, or diarrhea develop in over 30% of patients. In a 2019 randomized controlled trial of patients with refractory heartburn and confirmed reflux (acid or nonacid) despite twice-daily PPI therapy, fundoplication resulted in 67% adequate symptom relief at 1 year compared with 12–28% with continued medical therapy.

A minimally invasive magnetic artificial sphincter is FDA approved for the treatment of GERD in patients with hiatal hernias less than 3 cm in size. The device is made up of a flexible, elastic string of titanium beads (wrapped around a magnetic core) that is placed laparoscopically below the diaphragm at the gastroesophageal junction. The magnets are designed to open with pressures generated during swallowing but remain closed during gastroesophageal reflux events, which generate lower pressure than swallowing. In prospective clinical trials with up to 5 years of follow up, magnetic sphincter augmentation has demonstrated GERD symptom relief equivalent to laparoscopic fundoplication but far fewer side effects (long-term dysphagia 4–10%, bloating 8%, diarrhea 2%, nausea/vomiting 2%). In 2020, results were reported comparing magnetic sphincter augmentation with twice-daily PPI therapy in patients with GERD and moderate to severe regurgitation. After 1 year, sphincter augmentation led to significant improvement of regurgitation in 96% of patients and of GERD symptoms in 81% of patients compared with 19% and 8% of patients, respectively, treated with twice-daily PPIs. Given the excellent safety and efficacy data demonstrated with this device to date, it should be considered as an alternative to fundoplication surgery for patients with GERD, especially those with troublesome regurgitation, and hiatal hernias less than 3 cm in size.

Surgical treatment is not recommended for patients who are well controlled with medical therapies but should be considered for those with severe reflux disease who are unwilling to accept lifelong medical therapy due to its expense, inconvenience, or theoretical risks as well as for patients with proven refractory GERD symptoms or bothersome regurgitation despite PPI therapy. Gastric bypass (rather than fundoplication) should be considered for obese patients with GERD.

Several endoscopic procedures have been developed to treat GERD; however, none have found wide acceptance, largely due to limited long-term efficacy.

When to Refer

- Patients with typical GERD whose symptoms do not resolve with empiric management with a twice-daily PPI.
- Patients with suspected extraesophageal GERD symptoms that do not resolve with 3 months of twice-daily PPI therapy.
- Patients with significant dysphagia or other "alarm" symptoms for upper endoscopy.
- Patients with Barrett esophagus for endoscopic surveillance.
- Patients who have Barrett esophagus with dysplasia or early mucosal cancer.
- Surgical therapy is considered.

Bell R et al. Magnetic sphincter augmentation superior to proton pump inhibitors for regurgitation in a 1-year randomized trial. Clin Gastroenterol Hepatol. 2020;18:1736. [PMID: 31518717]

Desai M et al. Management of peptic strictures. Am J Gastroenterol. 2020;115:967. [PMID: 32618639]

Dhaliwal L et al. Neoplasia detection rate in Barrett's esophagus and its impact on missed dysplasia: results from a large population-based study. Clin Gastroenterol Hepatol. 2021;19:922. [PMID: 32707339]

Dunn CP et al. Understanding the GERD barrier. J Clin Gastroenterol. 2021;55:459. [PMID: 33883513]

Yanes M et al. Mortality, reoperation, and hospital stay within 90 days of primary and secondary antireflux surgery in a population-based multinational study. Gastroenterology. 2021;160:2283. [PMID: 33587926]

INFECTIOUS ESOPHAGITIS

ESSENTIALS OF DIAGNOSIS

- Immunosuppressed patient.
- Odynophagia, dysphagia, and chest pain.
- Endoscopy with biopsy establishes diagnosis.

General Considerations

Infectious esophagitis occurs most commonly in immunosuppressed patients. Patients with AIDS, solid organ transplants, leukemia, lymphoma, and those receiving immunosuppressive drugs are at particular risk for opportunistic infections. *Candida albicans*, herpes simplex, and CMV are the most common pathogens. *Candida* infection may occur also in patients who have uncontrolled diabetes and those being treated with systemic corticosteroids, radiation therapy, or systemic antibiotic therapy. Herpes simplex can affect normal hosts, in which case the infection is generally self-limited.

Clinical Findings

A. Symptoms and Signs

The most common symptoms are odynophagia and dysphagia. Substernal chest pain occurs in some patients. Patients with candidal esophagitis are sometimes asymptomatic. Oral thrush is present in only 75% of patients with candidal esophagitis but also occurs in 25–50% of patients with viral esophagitis and is therefore an unreliable indicator of the cause of esophageal infection. Patients with esophageal CMV infection may have infection at other sites such as the colon and retina. Oral ulcers (herpes labialis) are often associated with herpes simplex esophagitis.

B. Special Examinations

Treatment may be empiric. For diagnostic certainty, endoscopy with biopsy and brushings (for microbiologic and histopathologic analysis) is preferred because of its high diagnostic accuracy. The endoscopic signs of candidal esophagitis are diffuse, linear, yellow-white plaques adherent to the mucosa. CMV esophagitis is characterized by one to several large, shallow, superficial ulcerations. Herpes esophagitis results in multiple small, deep ulcerations.

Treatment

A. Candidal Esophagitis

Systemic therapy is required for esophageal candidiasis. An empiric trial of antifungal therapy is often administered without performing diagnostic endoscopy. Initial therapy is generally with fluconazole, 400 mg on day 1, then 200–400 mg/day orally for 14–21 days. Patients not responding to empiric therapy within 3–5 days should undergo endoscopy with brushings, biopsy, and culture to distinguish resistant fungal infection from other infections (eg, CMV, herpes). Esophageal candidiasis not responding to fluconazole therapy may be treated with itraconazole suspension (not capsules), 200 mg/day orally, or voriconazole, 200 mg orally twice daily. Refractory infection may be treated intravenously with caspofungin, 50 mg daily.

B. Cytomegalovirus Esophagitis

In patients with HIV infection, immune restoration with antiretroviral therapy is the most effective means of controlling CMV disease. Initial therapy is with ganciclovir, 5 mg/kg intravenously every 12 hours for 3–6 weeks. Neutropenia is a frequent dose-limiting side effect. Once resolution of symptoms occurs, it may be possible to complete the course of therapy with oral valganciclovir, 900 mg once daily.

Patients who either do not respond to or cannot tolerate ganciclovir are treated acutely with foscarnet, 90 mg/kg intravenously every 12 hours for 3–6 weeks. The principal toxicities are AKI, hypocalcemia, and hypomagnesemia.

C. Herpetic Esophagitis

Immunocompetent patients may be treated symptomatically and generally do not require specific antiviral therapy. Immunosuppressed patients may be treated with oral acyclovir, 400 mg orally five times daily, or 250 mg/m^2 intravenously every 8–12 hours, usually for 14–21 days. Oral famciclovir, 500 mg orally three times daily, or valacyclovir, 1 g twice daily, are also effective but more expensive than generic acyclovir. Nonresponders require therapy with foscarnet, 40 mg/kg intravenously every 8 hours for 21 days.

Prognosis

Most patients with infectious esophagitis can be effectively treated with complete symptom resolution. Depending on the patient's underlying immunodeficiency, relapse of symptoms off therapy can raise difficulties. Long-term suppressive therapy is sometimes required.

Hoversten P et al. Risk factors, endoscopic features, and clinical outcomes of cytomegalovirus esophagitis based on a 10-year analysis at a single center. Clin Gastroenterol. 2020;18:736. [PMID: 31077832]

Narasimhalu T et al. Educational case: infectious esophagitis. Acad Pathol. 2020;7:2374289520903438. [PMID: 32083170]

PILL-INDUCED ESOPHAGITIS

A number of different medications may injure the esophagus, presumably through direct, prolonged mucosal contact or mechanisms that disrupt mucosal integrity. The most commonly implicated are the NSAIDs, potassium chloride pills, quinidine, zalcitabine, zidovudine, alendronate and risedronate, emepronium bromide, iron, vitamin C, and antibiotics (doxycycline, tetracycline, clindamycin, trimethoprim-sulfamethoxazole). Because injury is most likely to occur if pills are swallowed without water or while supine, hospitalized or bed-bound patients are at greater risk. Symptoms include severe retrosternal chest pain, odynophagia, and dysphagia, often beginning several hours after taking a pill. These may occur suddenly and persist for days. Some patients (especially older patients) have relatively little pain, presenting with dysphagia. Endoscopy may reveal one to several discrete ulcers that may be shallow or deep. Chronic injury may result in severe esophagitis with stricture, hemorrhage, or perforation. Healing occurs rapidly when the offending agent is eliminated. To prevent pill-induced damage, patients should take pills with 4 oz of water and remain upright for 30 minutes after ingestion. Known offending agents should not be given to patients with esophageal dysmotility, dysphagia, or strictures.

Syed M. Pill-induced oesophagitis. Postgrad Med J. 2021;97:349. [PMID: 32423921]

BENIGN ESOPHAGEAL LESIONS

1. Mallory-Weiss Syndrome (Mucosal Laceration of Gastroesophageal Junction)

ESSENTIALS OF DIAGNOSIS

- Hematemesis; usually self-limited.
- Prior history of vomiting, retching in 50%.
- Endoscopy establishes diagnosis.

General Considerations

Mallory-Weiss syndrome is characterized by a nonpenetrating mucosal tear at the gastroesophageal junction that is hypothesized to arise from events that suddenly raise transabdominal pressure, such as lifting, retching, or vomiting. Alcoholism is a strong predisposing factor. Mallory-Weiss tears are responsible for approximately 5% of cases of upper GI bleeding.

Clinical Findings

A. Symptoms and Signs

Patients usually present with hematemesis with or without melena. A history of retching, vomiting, or straining is obtained in about 50% of cases.

B. Special Examinations

As with other causes of upper GI hemorrhage, upper endoscopy should be performed after the patient has been appropriately resuscitated. The diagnosis is established by identification of a 0.5- to 4-cm linear mucosal tear usually located either at the gastroesophageal junction or, more commonly, just below the junction in the gastric mucosa.

Differential Diagnosis

At endoscopy, other potential causes of upper GI hemorrhage are found in over 35% of patients with Mallory-Weiss tears, including peptic ulcer disease, erosive gastritis, arteriovenous malformations, and esophageal varices. Patients with underlying portal hypertension are at higher risk for continued or recurrent bleeding.

Treatment

Patients are initially treated as needed with fluid resuscitation and blood transfusions. Most patients stop bleeding spontaneously and require no therapy. Endoscopic hemostatic therapy is employed in patients who have continuing active bleeding. Injection with epinephrine (1:10,000), cautery with a bipolar or heater probe coagulation device, or mechanical compression of the artery by application of an endoclip or band is effective in 90–95% of cases. Angiographic arterial embolization or operative intervention is required in patients who fail endoscopic therapy.

He L et al. The prediction value of scoring systems in Mallory-Weiss syndrome patients. Medicine (Baltimore). 2019;98: e15751. [PMID: 31145291]

2. Eosinophilic Esophagitis

General Considerations

Eosinophilia of the esophagus may be caused by eosinophilic esophagitis and GERD (and, rarely, celiac disease, Crohn disease, and pemphigus).

Eosinophilic esophagitis is a disorder in which food or environmental antigens are thought to stimulate an inflammatory response. Initially recognized in children, it is increasingly identified in young or middle-aged adults (estimated prevalence 43/100,000). A history of allergies or atopic conditions (asthma, eczema, hay fever) is present in over half of patients.

Clinical Findings

Most adults have a long history of dysphagia for solid-foods or an episode of food impaction. Heartburn or chest pain may be present. Children may have abdominal pain, vomiting, or failure to thrive. On laboratory tests, a few have eosinophilia or elevated IgE levels. Barium swallow studies may demonstrate a small-caliber esophagus; focal or long, tapered strictures; or multiple concentric rings. However, endoscopy with esophageal biopsy and histologic evaluation is required to establish the diagnosis. Endoscopic appearances include **E**dema, concentric **R**ings ("trachealization"), **E**xudates (white plaques), **F**urrows (vertical lines), and **S**trictures (EREFS); however, the esophagus is grossly normal in up to 5% of patients. Multiple biopsies (4–8) from the proximal and distal esophagus should be obtained to demonstrate multiple (greater than 15/high-powered field) eosinophils in the mucosa. Consideration should be given to the disorders that may cause increased esophageal eosinophils, including hypereosinophilic syndrome, eosinophilic gastroenteritis, achalasia, connective tissue disorders, drug hypersensitivity, and Crohn disease. Skin testing for food allergies may be helpful to identify causative factors.

Treatment

The goals of therapy are improvement of symptoms, reduction of inflammation, and prevention and treatment of esophageal strictures. Treatment options include PPIs, topical corticosteroids, food elimination diets, and esophageal dilation. First-line therapy for most adults is a PPI orally twice daily for 2 months followed by repeat endoscopy and mucosal biopsy. Up to one-third of symptomatic patients with increased esophageal eosinophils have clinical and histologic improvement with PPI treatment. It is hypothesized that esophageal acid exposure may contribute to antigen-mediated eosinophilic inflammation. PPI therapy should be discontinued in patients with persistent symptoms and inflammation.

In patients with continued symptoms, optimal treatment is uncertain. Referral to an allergist for evaluation of coexisting atopic disorders and for testing for food and environmental allergens may be considered, but studies suggest limited predictive value in adults. Empiric elimination of suspected dietary allergens leads to clinical, endoscopic and histologic improvement in 50–70% of adults. The most common allergenic foods are dairy, eggs, wheat, and soy followed by peanuts and shellfish. With progressive reintroduction of each food group, the trigger food group may be identified in up to 85% of patients. Topical corticosteroids lead to symptom resolution in 70% of adults. Either budesonide in sucralose suspension, 1 mg, or powdered fluticasone, 880 mcg (from foil-lined inhaler diskus), is administered twice daily for 6–8 weeks with similar efficacy. Symptomatic relapse is common after discontinuation of therapy and may require maintenance topical corticosteroid therapy. Budesonide orodispersible tablets 0.5 or 1.0 mg twice daily are approved in Europe for initial and maintenance therapy of eosinophilic esophagitis but are not yet available in the United States. In a 2011 phase 3 randomized controlled trial of patients who achieved clinical and histologic remission after 6 weeks of budesonide orodispersible tablet 1.0 mg twice daily, 75% of participants who continued budesonide 0.5 mg or 1.0 mg twice daily for 48 weeks remained in remission compared with only 4.4% of patients given placebo. Esophageal candidiasis occurred in 13–18% of treated patients. Graduated dilation of strictures should be conducted in patients with dysphagia and strictures or narrow-caliber esophagus but should be performed cautiously because there is an increased risk of perforation and postprocedural chest pain.

Hirano I et al. AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters clinical guidelines for the management of eosinophilic esophagitis. Gastroenterology. 2020;158:1776. [PMID: 32359562]
Muir A et al. Eosinophilic esophagitis: a review. JAMA. 2021;326:1310. [PMID:34609446]
Rank MA et al. Technical review on the management of eosinophilic esophagitis: a report of the AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters. Gastroenterology. 2020;158:1789. [PMID: 32359563]
Straumann A et al. Budesonide orodispersible tablets maintain remission in a randomized, placebo-controlled trial of patients with eosinophilic esophagitis. Gastroenterology. 2020;159:1672. [PMID: 32721437]

3. Esophageal Webs & Rings

Esophageal webs are thin, diaphragm-like membranes of squamous mucosa that typically occur in the mid or upper esophagus and may be multiple. They may be congenital but also occur with eosinophilic esophagitis, graft-versus-host disease, pemphigoid, epidermolysis bullosa, pemphigus vulgaris, and, rarely, in association with iron deficiency anemia (Plummer-Vinson syndrome). Esophageal "Schatzki" rings are smooth, circumferential, thin (less than 4 mm in thickness) mucosal structures located in the distal esophagus at the squamocolumnar junction. Their pathogenesis is controversial. They are associated in nearly all cases with a hiatal hernia, and reflux symptoms are common, suggesting that acid gastroesophageal reflux may be contributory in many cases. Most webs and rings are

over 20 mm in diameter and are asymptomatic. Solid food dysphagia most often occurs with rings less than 13 mm in diameter. Characteristically, dysphagia is intermittent and not progressive. Large poorly chewed food boluses such as beefsteak are most likely to cause symptoms. Obstructing boluses may pass by drinking extra liquids or after regurgitation. In some cases, an impacted bolus must be extracted endoscopically. Esophageal webs and rings are best visualized using a barium esophagogram with full esophageal distention. Endoscopy is less sensitive than barium esophagography.

The majority of symptomatic patients with a single ring or web can be effectively treated with the passage of bougie or endoscopic balloon dilators to disrupt the lesion or endoscopic electrosurgical incision of the ring. A minimum lumen diameter of 15–18 mm achieves symptom remission in most patients. A single dilation may suffice, but repeat dilations are required in many patients. Patients who have heartburn or who require repeated dilation should receive long-term acid suppressive therapy with a PPI.

Vermeulen BD et al. Risk factors and clinical outcomes of endoscopic dilation in benign esophageal strictures: a long-term follow-up study. Gastrointest Endosc. 2020;91:1058. [PMID: 31917167]

4. Zenker Diverticulum

Zenker diverticulum is a protrusion of pharyngeal mucosa that develops at the pharyngoesophageal junction between the inferior pharyngeal constrictor and the cricopharyngeus. The cause is believed to be loss of elasticity of the upper esophageal sphincter, resulting in restricted opening during swallowing. Symptoms of dysphagia and regurgitation tend to develop insidiously over years in older, predominantly male patients. Initial symptoms include vague oropharyngeal dysphagia with coughing or throat discomfort. As the diverticulum enlarges and retains food, patients may note halitosis, spontaneous regurgitation of undigested food, nocturnal choking, gurgling in the throat, or a protrusion in the neck. Complications include aspiration pneumonia, bronchiectasis, and lung abscess. The diagnosis is best established by a videoesophagography.

Symptomatic patients require cricopharyngeal myotomy with incision of the septum between the diverticulum and esophagus. Minimally invasive intraluminal approaches that use flexible endoscopes or rigid esophagoscopes are preferred. Significant improvement occurs in over 90% of patients with a recurrence rate of 11%. Giant diverticula require surgical transcervical myotomy with diverticulectomy. Small asymptomatic diverticula may be observed.

Brewer Gutierrez OI et al. Zenker's diverticulum per-oral endoscopic myotomy techniques: changing paradigms. Gastroenterology. 2019;156:2134. [PMID: 30851303]
Jirapinyo P et al. Devices and techniques for flexible endoscopic management of Zenker's diverticulum (with videos). Gastrointest Endosc. 2021;94:3. [PMID: 33926711]
Wagh MS et al. How to approach a patient with Zenker's diverticulum. Gastroenterology. 2021;160:10. [PMID: 33220254]

5. Esophageal Varices

ESSENTIALS OF DIAGNOSIS

- Develop secondary to portal hypertension.
- Found in 50% of patients with cirrhosis.
- One-third of patients with varices develop upper GI bleeding.
- Diagnosis established by upper endoscopy.

General Considerations

Esophageal varices are dilated submucosal veins that develop in patients with underlying portal hypertension and that may result in serious upper GI bleeding. The causes of portal hypertension are discussed in Chapter 16. Under normal circumstances, there is a 2–6 mm Hg pressure gradient between the portal vein and the inferior vena cava. When the gradient exceeds 10–12 mm Hg, significant portal hypertension exists. Esophageal varices are the most common cause of important GI bleeding due to portal hypertension, though gastric varices and, rarely, intestinal varices may also bleed. Bleeding from esophageal varices most commonly occurs in the distal 5 cm of the esophagus.

The most common cause of portal hypertension is cirrhosis. Approximately 50% of patients with cirrhosis have esophageal varices. Bleeding from varices occurs in 30% of patients with esophageal varices. In the absence of any treatment, variceal bleeding spontaneously stops in about 50% of patients. Patients surviving this bleeding episode have a 60% chance of recurrent variceal bleeding, usually within the first 6 weeks. With current therapies, the in-hospital mortality rate associated with bleeding esophageal varices is 15%.

A number of factors have been identified that may portend an increased risk of bleeding from esophageal varices. The most important are (1) the size of the varices; (2) the presence at endoscopy of red wale markings (longitudinal dilated venules on the varix surface); (3) the severity of liver disease (as assessed by Child scoring); and (4) active alcohol abuse—patients with cirrhosis who continue to drink have an extremely high risk of variceal bleeding.

Clinical Findings

A. Symptoms and Signs

Patients with bleeding esophageal varices present with symptoms and signs of acute GI hemorrhage. (See Acute Upper GI Bleeding, above.) In some cases, there may be preceding retching or dyspepsia attributable to alcoholic gastritis or withdrawal. Varices per se do not cause symptoms of dyspepsia, dysphagia, or retching. Variceal bleeding usually is severe, resulting in hypovolemia manifested by postural vital signs or shock. But 20% of patients with chronic liver disease in whom bleeding develops have a nonvariceal source of bleeding.

B. Laboratory Findings

These are identical to those listed above in the section on Acute Upper GI Bleeding.

Initial Management

A. Acute Resuscitation

The initial management of patients with acute upper GI bleeding is also discussed in the section on Acute Upper GI Bleeding. Variceal hemorrhage is life-threatening; rapid assessment and resuscitation with fluids or blood products are essential. Overtransfusion should be avoided because it leads to increased central and portal venous pressures, increasing the risk of rebleeding. Most patients with bleeding esophageal varices have advanced liver disease with coagulopathy due to thrombocytopenia; deficiencies of liver-derived clotting factors I (fibrinogen), II, VII, IX, and X; and accelerated intravascular fibrinolysis. The INR does not provide an accurate reflection of coagulopathy in advanced liver disease. Fresh frozen plasma should not be administered routinely in stable patients with an elevated INR because it has no proven benefit but does have potential harms, including increased portal pressures and risk of portal vein or deep venous thrombosis. In patients with decompensated cirrhosis and active severe upper GI bleeding, platelet transfusion is recommended for platelet counts below 50,000/mcL (50×10^9/L) and fresh frozen plasma may be considered for INRs greater than 1.8. Recombinant factor VIIa has not demonstrated efficacy in controlled studies and is not recommended. The role of prothrombin complex concentrates requires further study. Patients with advanced liver disease are at high risk for poor outcome regardless of the bleeding source and should be in an ICU.

B. Pharmacologic Therapy

1. Antibiotic prophylaxis—Cirrhotic patients admitted with upper GI bleeding have a greater than 50% chance of developing a severe bacterial infection during hospitalization—such as bacterial peritonitis, pneumonia, or UTI. Most infections are caused by gram-negative organisms of gut origin. Prophylactic administration of intravenous third-generation cephalosporins (eg, ceftriaxone, 1 g/day) for 5–7 days reduces the risk of serious infection to 10–20% as well as hospital mortality, especially in patients with Child-Pugh class C cirrhosis.

2. Vasoactive drugs—Octreotide and somatostatin infusions reduce portal pressures in ways that are poorly understood. Octreotide (50 mcg intravenous bolus followed by 50 mcg/hour) or somatostatin (250 mcg/hour)—not available in the United States—reduces splanchnic and hepatic blood flow and portal pressures in cirrhotic patients. Both agents appear to provide acute control of variceal bleeding in up to 80% of patients although neither has been shown to reduce mortality. Combined treatment with octreotide or somatostatin infusion and endoscopic therapy with band ligation (or sclerotherapy) is superior to either modality alone in controlling acute bleeding and early rebleeding, and it may improve survival. In patients with advanced liver disease and upper GI hemorrhage, it is reasonable to initiate therapy with octreotide or somatostatin on admission and continue for 3–5 days if varices are confirmed by endoscopy. If bleeding is determined by endoscopy not to be secondary to portal hypertension, the infusion can be discontinued.

Terlipressin, 1–2 mg intravenously every 4 hours (not available in the United States), is a synthetic vasopressin analog that causes a significant and sustained reduction in portal and variceal pressures while preserving renal perfusion. Where available, terlipressin may be preferred to somatostatin or octreotide. Terlipressin is contraindicated in patients with significant coronary, cerebral, or peripheral vascular disease.

3. Vitamin K—In cirrhotic patients with an abnormal prothrombin time, vitamin K (10 mg intravenously) should be administered.

4. Lactulose—Encephalopathy may complicate an episode of GI bleeding in patients with severe liver disease. In patients with encephalopathy, lactulose should be administered in a dosage of 30 mL orally every 1–2 hours until evacuation occurs then reduced to 15–45 mL/hour every 8–12 hours as needed to promote two or three bowel movements daily. (See Chapter 16.)

C. Emergent Endoscopy

Emergent endoscopy is performed after the patient's hemodynamic status has been appropriately stabilized (usually within 12–24 hours). In patients with active bleeding, endotracheal intubation is commonly performed to protect against aspiration during endoscopy. An endoscopic examination is performed to exclude other or associated causes of upper GI bleeding such as Mallory-Weiss tears, peptic ulcer disease, and portal hypertensive gastropathy. In many patients, variceal bleeding has stopped spontaneously by the time of endoscopy, and the diagnosis of variceal bleeding is made presumptively. Immediate endoscopic treatment of the varices generally is performed with banding. In clinical practice, sclerotherapy is now seldom used. These techniques arrest active bleeding in 80–90% of patients and reduce the chance of in-hospital recurrent bleeding to about 20%.

If banding is undertaken, repeat sessions are scheduled at intervals of 2–4 weeks until the varices are obliterated or reduced to a small size. For patients with platelet counts less than 50,000/mcL (50×10^9/L), consideration should be given to preprocedure administration of avatrombopag, an FDA-approved oral thrombopoietin receptor agonist. In phase 3 clinical trials at a dose of 40–60 mg/day for 5 consecutive days beginning 10–13 days prior to endoscopy, 68% of patients with baseline platelet counts less than 40,000/mcL (40×10^9/L) and 88% with baseline counts 40,000–50,000/mcL achieved platelet counts greater than 50,000/mcL (50×10^9/L) and avoided periprocedural platelet transfusions.

D. Balloon Tube Tamponade

In patients with massive variceal GI bleeding, mechanical tamponade with specially designed nasogastric tubes containing large gastric and esophageal balloons (Minnesota

or Sengstaken-Blakemore tubes) may provide initial control of hemorrhage in 60–90% of patients. Balloon tamponade is used as a temporizing measure only in patients with bleeding that cannot be controlled with pharmacologic or endoscopic techniques until more definitive decompressive therapy (eg, TIPS) can be provided.

E. Portal Decompressive Procedures

In the 10–20% of patients with variceal bleeding that cannot be controlled with pharmacologic or endoscopic therapy, emergency portal decompression may be considered.

1. Transvenous intrahepatic portosystemic shunts (TIPS)—Over a wire that is passed through a catheter inserted in the jugular vein, an expandable wire mesh stent (8–12 mm in diameter) is passed through the liver parenchyma, creating a portosystemic shunt from the portal vein to the hepatic vein. TIPS can control acute hemorrhage in over 90% of patients actively bleeding from gastric or esophageal varices. However, when TIPS is performed in the actively bleeding patient, the mortality approaches 40%, especially in patients requiring ventilatory support or blood pressure support and patients with renal insufficiency, bilirubin greater than 3 mg/dL, or encephalopathy. Therefore, TIPS should be considered in the 10–20% of patients with acute variceal bleeding that cannot be controlled with pharmacologic and endoscopic therapy, but it may not be warranted in patients with a particularly poor prognosis.

2. Emergency portosystemic shunt surgery—Emergency portosystemic shunt surgery is associated with a 40–60% mortality rate. At centers where TIPS is available, emergency portosystemic shunts are no longer performed.

Prevention of Rebleeding

Once the initial bleeding episode has been controlled, therapy is warranted to reduce the high risk (60%) of rebleeding.

A. Combination Beta-Blockers and Variceal Band Ligation

Nonselective beta-adrenergic blockers (propranolol, nadolol) reduce the risk of rebleeding from esophageal varices to about 40%. Likewise, long-term treatment with band ligation reduces the incidence of rebleeding to about 30%. In most patients, two to six treatment sessions (performed at 2- to 4-week intervals) are needed to eradicate the varices.

Meta-analyses of randomized controlled trials suggest that a *combination* of band ligation plus beta-blockers is superior to either variceal band ligation alone (RR 0.68) or beta-blockers alone (RR 0.71). Therefore, combination therapy is recommended for patients without contraindications to beta-blockers. Recommended starting doses of beta-blockers are propranolol (20 mg orally twice daily), long-acting propranolol (60 mg orally once daily), or nadolol (20–40 mg orally once daily), with gradual increases in the dosage every 1–2 weeks until the heart rate falls by 25% or reaches 55–60 beats/minute, provided the systolic blood pressure remains above 90 mm Hg and the patient has no side effects. The average dosage of long-acting propranolol is 120 mg once daily and for nadolol, 80 mg once daily. One-third of patients with cirrhosis are intolerant of beta-blockers, experiencing fatigue or hypotension. Drug administration at bedtime may reduce the frequency and severity of side effects.

B. Transvenous Intrahepatic Portosystemic Shunt

TIPS has resulted in a significant reduction in recurrent bleeding compared with endoscopic sclerotherapy or band ligation—either alone or in combination with beta-blocker therapy. At 1 year, rebleeding rates in patients treated with TIPS versus various endoscopic therapies average 20% and 40%, respectively. However, TIPS was also associated with a higher incidence of encephalopathy (35% vs 15%) and did not result in a decrease in mortality. Another limitation of TIPS is that stenosis and thrombosis of the stents occur in the majority of patients over time with a consequent risk of rebleeding. Given these problems, TIPS should be reserved for patients who have recurrent (two or more) episodes of variceal bleeding that have failed endoscopic or pharmacologic therapies. TIPS is also useful in patients with recurrent bleeding from gastric varices or portal hypertensive gastropathy (for which endoscopic therapies cannot be used). TIPS is likewise considered in patients who are noncompliant with other therapies or who live in remote locations (without access to emergency care).

C. Surgical Portosystemic Shunts

Shunt surgery has a significantly lower rate of rebleeding compared with endoscopic therapy but also a higher incidence of encephalopathy. With the advent and widespread adoption of TIPS, surgical shunts are seldom performed.

D. Liver Transplantation

Candidacy for orthotopic liver transplantation should be assessed in all patients with chronic liver disease and bleeding due to portal hypertension. Transplant candidates should be treated with band ligation or TIPS to control bleeding pretransplant.

Prevention of First Episodes of Variceal Bleeding

Among patients with varices that have not previously bled, bleeding occurs in 12% of patients each year, with a lifetime risk of 30%. Because of the high mortality rate associated with variceal hemorrhage, prevention of the initial bleeding episode is desirable. Therefore, it is recommended that patients with chronic liver disease with compensated cirrhosis or suspected cirrhosis should undergo diagnostic endoscopy or capsule endoscopy to determine whether varices are present. Transient elastography (FibroScan) is a noninvasive method for assessing liver stiffness and fibrosis that may be used to stratify patients at high risk for varices (who may benefit from endoscopy) versus those at low risk (in whom endoscopy is not needed). Varices are present in 40% of patients with Child-Pugh class A cirrhosis and in 85% with Child-Pugh class C cirrhosis. In patients without

varices on screening endoscopy, a repeat endoscopy is recommended in 3 years, since varices develop in 8% of patients per year. Patients with varices have a higher risk of bleeding if they have varices larger than 5 mm, varices with red wale markings, or Child-Pugh class B or C cirrhosis. The risk of bleeding in patients with varices smaller than 5 mm is 5% per year and with large varices is 15–20% per year. Patients with small varices without red wale marks and compensated (Child-Pugh class A) cirrhosis have a low risk of bleeding; hence, prophylaxis is unnecessary, but endoscopy should be repeated in 1–2 years to reassess size.

Nonselective beta-adrenergic blockers are recommended to reduce the risk of first variceal hemorrhage in patients with medium/large varices and patients with small varices who either have variceal red wale marks or advanced cirrhosis (Child-Pugh class B or C). (See Combination Beta-Blockers and Variceal Band Ligation, above.) Band ligation is not recommended for small varices due to technical difficulties in band application. Prophylactic band ligation may be preferred over beta-blockers for patients at higher risk for bleeding, especially patients with medium/large varices with red wale markings or with advanced cirrhosis (Child-Pugh class B or C) as well as patients with contraindications to or intolerance of beta-blockers.

When to Refer

- All patients with upper GI bleeding and suspected varices should be evaluated by a physician skilled in therapeutic endoscopy.
- Patients being considered for TIPS procedures or liver transplantation.
- Patients with cirrhosis for endoscopic evaluation for varices.

When to Admit

All patients with acute upper GI bleeding and suspected cirrhosis should be admitted to an ICU.

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ESOPHAGEAL MOTILITY DISORDERS

1. Achalasia

ESSENTIALS OF DIAGNOSIS

- Gradual, progressive dysphagia for solids and liquids.
- Regurgitation of undigested food.
- Barium esophagogram with "bird's beak" distal esophagus.
- Esophageal manometry confirms diagnosis.

General Considerations

Achalasia is an idiopathic motility disorder characterized by loss of peristalsis in the distal two-thirds (smooth muscle) of the esophagus and impaired relaxation of the LES. There appears to be denervation of the esophagus resulting primarily from loss of nitric oxide–producing inhibitory neurons in the myenteric plexus. The cause of the neuronal degeneration is unknown.

Clinical Findings

A. Symptoms and Signs

There is a steady increase in the incidence of achalasia with age; however, it can be seen in individuals as young as 25 years. Patients complain of the gradual onset of dysphagia for solid foods and, in the majority, for liquids also. Symptoms at presentation may have persisted for months to years. Substernal discomfort or fullness may be noted after eating. Many patients eat more slowly and adopt specific maneuvers such as lifting the neck or throwing the shoulders back to enhance esophageal emptying. Regurgitation of undigested food is common and may occur during meals or up to several hours later. Nocturnal regurgitation can provoke coughing or aspiration. Up to 50% of patients report substernal chest pain that is unrelated to meals or exercise and may last up to hours. Weight loss is common. Physical examination is unhelpful.

B. Imaging

Chest radiographs may show an air-fluid level in the enlarged, fluid-filled esophagus. Barium esophagography discloses characteristic findings, including esophageal dilation, loss of esophageal peristalsis, poor esophageal emptying, and a smooth, symmetric "bird's beak" tapering of the distal esophagus. Five minutes after ingestion of 8 oz of barium, a column height of more than 2 cm has a sensitivity and specificity of greater than 85% in differentiating achalasia from other causes of dysphagia. Without treatment, the esophagus may become markedly dilated ("sigmoid esophagus").

C. Special Examinations

After esophagography, endoscopy is always performed to evaluate the distal esophagus and gastroesophageal junction

to exclude a distal stricture or a submucosal infiltrating carcinoma. The diagnosis is confirmed by high-resolution esophageal manometry demonstrating absence of normal peristalsis and impaired esophagogastric junction relaxation after swallowing. An integrated post-swallow relaxation pressure greater than 15 mm Hg has a diagnostic sensitivity of 97%. Three achalasia subtypes are recognized based on esophageal contractility and pressure patterns: types I and II (both with 100% failed peristalsis) and type III (failed peristalsis with 20% or more distal premature "spastic" contractions).

Differential Diagnosis

Chagas disease is associated with esophageal dysfunction that is indistinguishable from idiopathic achalasia and should be considered in patients from endemic regions (Central and South America); it is becoming more common in the southern United States. Primary or metastatic tumors can invade the gastroesophageal junction, resulting in a picture resembling that of achalasia, called "pseudoachalasia." Endoscopic ultrasonography and chest CT may be required to examine the distal esophagus in suspicious cases.

Treatment

Several effective treatment options are available, all of which promote improved esophageal emptying by lowering distal esophageal pressure either through endoscopic injection with botulinum toxin or disruption of the LES by pneumatic balloon dilation or cardioesophageal myotomy (surgical or endoscopic).

A. Botulinum Toxin Injection

Endoscopically guided injection of botulinum toxin directly into the LES results in a marked reduction in LES pressure with initial improvement in symptoms in 65–85% of patients. However, symptom relapse occurs in over 50% of patients within 6–9 months and in all patients within 2 years. Because it is inferior to pneumatic dilation therapy and surgery in producing sustained symptomatic relief, this therapy is most appropriate for patients with comorbidities who are poor candidates for more invasive procedures.

B. Pneumatic Dilation

Over 80% of patients derive good to excellent relief of dysphagia after one to three sessions of pneumatic dilation of the LES. Dilation is less effective in patients who are younger than age 45, have the type III variant, or have a dilated esophagus. Perforations occur in less than 3% of dilations but infrequently require operative repair. In a 2021 network meta-analysis of nine randomized controlled trials, laparoscopic Heller myotomy and POEM were not significantly different in treatment success but both were superior to pneumatic dilation. Patients who do not respond to initial treatment with pneumatic dilation may be treated with cardiomyotomy (Heller or POEM).

C. Surgical Heller Cardiomyotomy

A modified Heller cardiomyotomy of the LES and cardia (usually performed with a laparoscopic approach) results in symptomatic improvement in approximately 90% of patients. Because gastroesophageal reflux develops in up to 20% of patients after myotomy, most surgeons also perform an antireflux procedure (fundoplication), and most patients are prescribed a once-daily PPI. Symptoms recur in greater than 5–15% of cases within 10 years but usually respond to pneumatic dilation. A 2017 systematic review of five randomized comparative cardiomyotomy trials detected a higher clinical success rate after 1 year with laparoscopic myotomy than Heller myotomy (RR 1.14) but no significant differences after 2–5 years.

D. Per Oral Endoscopic Myotomy (POEM)

POEM is a less invasive endoscopic procedure in which the endoscope dissects through the submucosal space to the lower esophageal sphincter, where the circular muscle fibers of the cardia and distal esophagus are incised. Because a fundoplication is not performed, long-term antisecretory therapy for gastroesophageal reflux with a PPI is required in most patients. POEM may be the preferred treatment modality for type III achalasia (where a longer myotomy of the distal esophagus is indicated). A randomized controlled trial of 221 patients with achalasia showed that satisfactory symptom improvement was equivalent both in patients treated with POEM (83%) and in those treated with surgical myotomy (81.7%) 2 years after treatment. Serious adverse events occurred in 2.7% of patients treated with POEM and 7.3% with surgical myotomy, but postoperative reflux esophagitis was higher with POEM (44%) than with surgical myotomy (29%).

In summary, optimal treatment of achalasia depends on the patient's age, achalasia subtype, provider's expertise, and patient's preferences or concerns regarding surgery or posttreatment gastroesophageal reflux.

Management of Refractory Achalasia

Complete esophagectomy or percutaneous gastrostomy is required in the 1% of patients in whom massive dilation of the esophagus (megaesophagus) develops despite dilation or myotomy. In megaesophagus, dysphagia, food retention, and regurgitation may decrease nutrition and quality of life and increase risk of aspiration.

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2. Other Primary Esophageal Motility Disorders

Clinical Findings

A. Symptoms and Signs

Abnormalities in esophageal motility may cause dysphagia or chest pain. Dysphagia for liquids as well as solids tends to be intermittent and nonprogressive. Periods of normal swallowing may alternate with periods of dysphagia, which usually is mild though bothersome—rarely severe enough to result in significant alterations in lifestyle or weight loss. Dysphagia may be provoked by stress, large boluses of food, or hot or cold liquids. Some patients may experience anterior chest pain that may be confused with angina pectoris but usually is nonexertional. The pain generally is unrelated to eating. (See Chest Pain of Undetermined Origin, below.)

B. Diagnostic Tests

The evaluation of suspected esophageal motility disorders includes barium esophagography, upper endoscopy, and, in some cases, esophageal manometry. Barium esophagography is useful to exclude mechanical obstruction and to evaluate esophageal motility. The presence of simultaneous contractions (spasm), disordered or failed peristalsis, or delayed emptying supports a diagnosis of esophageal dysmotility. Upper endoscopy also is performed to exclude a mechanical obstruction (as a cause of dysphagia) and to look for evidence of erosive reflux esophagitis (a common cause of chest pain) or eosinophilic esophagitis (confirmed by esophageal biopsy). Manometry is not routinely used for mild to moderate symptoms because the findings seldom influence further medical management, but it may be useful in patients with persistent, disabling dysphagia to exclude achalasia and to look for other disorders of esophageal motility. These include esophagogastric junction outflow obstruction, spastic esophageal disorders (distal esophageal spasm and hypercontractile ["jackhammer"] esophagus), and esophageal hypomotility (ineffective or failed peristalsis). The further evaluation of noncardiac chest pain is discussed below.

Treatment

For patients with mild symptoms of dysphagia, therapy is directed at symptom reduction and reassurance. Patients should be instructed to chew carefully, eat more slowly, and take smaller bites of food with liquids. Because unrecognized gastroesophageal reflux may cause dysphagia, a trial of a PPI (esomeprazole 40 mg, lansoprazole 30 mg) orally twice daily should be administered for 4–8 weeks. Opioids may exacerbate esophageal dysmotility and should be discontinued, if possible. No medications have been shown to improve symptoms in patients with esophageal hypomotility. Treatment of patients with severe dysphagia or chest pain attributed to spastic disorders is empiric. Uncontrolled studies report benefit with (1) smooth muscle relaxants (isosorbide [10–20 mg four times daily] or nitroglycerin [0.4 mg sublingually as needed]); (2) calcium channel blockers (nifedipine [10 mg] or diltiazem [60–90 mg] 30–45 minutes before meals); (3) phosphodiesterase type 5 inhibitors (eg, sildenafil); (4) botulinum toxin injection into the lower esophagus; (5) esophageal dilation; or (6) POEM.

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Mittal R et al. Esophageal motility disorders and gastroesophageal reflux disease. N Engl J Med. 2020;383:1961. [PMID: 33176086]
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DISEASES OF THE STOMACH & DUODENUM

(See Chapter 39 **for Gastric Cancers.)**

GASTRITIS & GASTROPATHY

The term "gastropathy" should be used to denote conditions in which there is epithelial or endothelial damage without inflammation, and "gastritis" should be used to denote conditions in which there is histologic evidence of inflammation. In clinical practice, the term "gastritis" is commonly applied to three categories: (1) erosive and hemorrhagic "gastritis" (gastropathy); (2) nonerosive, nonspecific (histologic) gastritis; and (3) specific types of gastritis, characterized by distinctive histologic and endoscopic features diagnostic of specific disorders.

1. Erosive & Hemorrhagic "Gastritis" (Gastropathy)

ESSENTIALS OF DIAGNOSIS

- Most commonly seen in alcoholic or critically ill patients, or patients taking NSAIDs.
- Often asymptomatic; may cause epigastric pain, nausea, and vomiting.
- May cause hematemesis; usually insignificant bleeding.

General Considerations

The most common causes of erosive gastropathy are medications (especially NSAIDs), alcohol, stress due to severe medical or surgical illness, and portal hypertension ("portal gastropathy"). Major risk factors for stress gastritis include mechanical ventilation, coagulopathy, trauma, burns, shock, sepsis, CNS injury, liver failure, kidney disease, and multiorgan failure. The use of enteral nutrition reduces the risk of stress-related bleeding. Uncommon

causes of erosive gastropathy include ischemia, caustic ingestion, and radiation. Erosive and hemorrhagic gastropathy typically are diagnosed at endoscopy, often being performed because of dyspepsia or upper GI bleeding. Endoscopic findings include subepithelial hemorrhages, petechiae, and erosions. These lesions are superficial, vary in size and number, and may be focal or diffuse. There usually is no significant inflammation on histologic examination.

Clinical Findings

A. Symptoms and Signs

Erosive gastropathy is usually asymptomatic. Symptoms, when they occur, include anorexia, epigastric pain, nausea, and vomiting. There is poor correlation between symptoms and the number or severity of endoscopic abnormalities. The most common clinical manifestation of erosive gastritis is upper GI bleeding, which presents as hematemesis, "coffee grounds" emesis, or bloody aspirate in a patient receiving nasogastric suction, or as melena. Because erosive gastritis is superficial, hemodynamically significant bleeding is rare.

B. Laboratory Findings

The laboratory findings are nonspecific. The hematocrit is low if significant bleeding has occurred; iron deficiency may be found.

C. Special Examinations

Upper endoscopy is the most sensitive method of diagnosis. Although bleeding from gastritis is usually insignificant, it cannot be distinguished on clinical grounds from more serious lesions such as peptic ulcers or esophageal varices. Hence, endoscopy is generally performed within 24 hours in patients with upper GI bleeding to identify the source.

Differential Diagnosis

Epigastric pain may be due to peptic ulcer, gastroesophageal reflux, gastric cancer, biliary tract disease, food poisoning, viral gastroenteritis, and functional dyspepsia. With severe pain, one should consider a perforated or penetrating ulcer, pancreatic disease, esophageal rupture, ruptured aortic aneurysm, gastric volvulus, GI ischemia, and myocardial ischemia. Causes of upper GI bleeding include peptic ulcer disease, esophageal varices, Mallory-Weiss tear, and angioectasias.

Specific Causes & Treatment

A. Stress Gastritis

1. Prophylaxis—Stress-related mucosal erosions and subepithelial hemorrhages may develop within 72 hours in critically ill patients. Clinically overt bleeding occurs in 6% of ICU patients, but clinically important bleeding in less than 1.5%. Bleeding is associated with a higher mortality rate but is seldom the cause of death. Two of the most important risk factors for bleeding are coagulopathy (platelets less than 50,000/mcL [50×10^9/L] or INR greater than 1.5) and respiratory failure with the need for mechanical ventilation for over 48 hours. When these two risk factors are absent, the risk of significant bleeding is only 0.1%. Other risk factors include traumatic brain injury, severe burns, sepsis, shock, liver disease, and prior history of peptic ulcer disease and GI bleeding. Early enteral tube feeding may decrease the risk of significant bleeding.

Prophylaxis should be routinely administered to critically ill patients with risk factors for significant bleeding upon admission. Prophylactic suppression of gastric acid with H_2-receptor antagonists (intravenous) or PPIs (oral or intravenous) have both been shown to reduce the incidence of clinically overt and significant bleeding. A meta-analysis of 57 randomized controlled trials suggested that PPIs were more effective than H_2-receptor antagonists in reducing clinically significant bleeding (OR 0.38) but may increase the risk of pneumonia (OR 1.27). A 2020 randomized clinical trial of 26,828 patients in 50 ICUs requiring mechanical ventilation reported a lower incidence of clinically significant bleeding in patients given prophylactic PPIs (1.3%) than in those given H_2-antagonists (1.8%) but a nonsignificant higher mortality (HR, 1.05; 95% CI, 1.00–1.10).

The optimal, cost-effective prophylactic regimen remains uncertain; hence, clinical practices vary. For patients with nasoenteric tubes, immediate-release omeprazole (40 mg at 1 and 6 hours on day 1; then 40 mg once daily beginning on day 2) may be preferred because of lower cost and ease of administration. For patients requiring intravenous administration, continuous intravenous infusions of H_2-receptor antagonists provide adequate control of intragastric pH in most patients in the following doses over 24 hours: cimetidine (900–1200 mg) or famotidine (20 mg). Alternatively, intravenous PPIs, although more expensive, may be preferred due to superior efficacy. The optimal dosing of intravenous PPIs is uncertain; however, in clinical trials pantoprazole doses ranging from 40 mg to 80 mg and administered every 8–24 hours appear equally effective.

2. Treatment—Once bleeding occurs, patients should receive continuous infusions of a PPI (esomeprazole or pantoprazole, 80 mg intravenous bolus, followed by 8 mg/hour continuous infusion) as well as sucralfate suspension, 1 g orally every 4 to 6 hours. Endoscopy should be performed in patients with clinically significant bleeding to look for treatable causes, especially stress-related peptic ulcers with active bleeding or visible vessels. When bleeding arises from diffuse gastritis, endoscopic hemostasis techniques are not helpful.

B. NSAID Gastritis

Of patients receiving NSAIDs in clinical trials, 25–50% have gastritis and 10–20% have ulcers at endoscopy; however, symptoms of significant dyspepsia develop in about 5%. NSAIDs that are more selective for the cyclooxygenase (COX)-2 enzyme ("coxibs"), such as celecoxib, etodolac, and meloxicam, decrease the incidence of endoscopically visible ulcers by approximately 75% and significant ulcer complications by up to 50% compared with nonselective NSAIDs (nsNSAIDs). COX-2 selective NSAIDs are associated with increased risk of cardiovascular complications

and therefore should be used with caution in patients with cardiovascular risk factors (see Peptic Ulcer Disease – NSAID-Induced Ulcers).

Dyspepsia is increased 1.5- to 2-fold with both nsNSAID and coxib use. However, dyspeptic symptoms correlate poorly with mucosal abnormalities (erosions or ulcers) or the development of adverse clinical events (ulcer bleeding or perforation). Given the frequency of dyspeptic symptoms in patients taking NSAIDs, it is neither feasible nor desirable to investigate all such cases. Patients with "alarm" symptoms or signs, such as severe pain, weight loss, vomiting, GI bleeding, or anemia, should undergo diagnostic upper endoscopy. For other patients, symptoms may improve with discontinuation of the agent, reduction to the lowest effective dose, or administration with meals. PPIs have demonstrated efficacy in controlled trials for the treatment of NSAID-related dyspepsia and superiority to H_2-receptor antagonists for healing of NSAID-related ulcers even in the setting of continued NSAID use. Therefore, an empiric 2- to 4-week trial of an oral PPI (omeprazole, rabeprazole, or esomeprazole, 20–40 mg/day; lansoprazole or dexlansoprazole, 30 mg/day; pantoprazole, 40 mg/day) is recommended for patients with NSAID-related dyspepsia, especially those in whom continued NSAID treatment is required. If symptoms do not improve, diagnostic upper endoscopy should be conducted.

C. Alcoholic Gastritis

Excessive alcohol consumption may lead to dyspepsia, nausea, emesis, and minor hematemesis—a condition sometimes labeled "alcoholic gastritis." However, it is not proven that alcohol alone actually causes significant erosive gastritis. Therapy with H_2-receptor antagonists, PPIs, or sucralfate for 2–4 weeks often is empirically prescribed.

D. Portal Hypertensive Gastropathy

Portal hypertension commonly results in gastric mucosal and submucosal congestion of capillaries and venules, which is correlated with the severity of the portal hypertension and underlying liver disease. Usually asymptomatic, it may cause chronic GI bleeding in 10% of patients and, less commonly, clinically significant bleeding with hematemesis. Treatment with propranolol or nadolol reduces the incidence of recurrent acute bleeding by lowering portal pressures. Patients who fail propranolol therapy may be successfully treated with portal decompressive procedures (see section above on treatment of esophageal varices).

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2. Nonerosive, Nonspecific Gastritis & Intestinal Metaplasia

Nonerosive gastritis is characterized by histologic inflammation. The main types of nonerosive gastritis are those due to *H pylori* infection, those associated with pernicious anemia, and eosinophilic gastritis, and possibly other genetic and environmental factors (see Specific Types of Gastritis below). The diagnosis of nonerosive gastritis is based on histologic assessment of mucosal biopsies. Endoscopic findings are normal in many cases and do not reliably predict the presence of histologic inflammation. While clinically silent in most patients, ongoing inflammation and glandular destruction may lead to patchy or diffuse atrophy of the normal cardia, fundic or antral mucosa with subsequent development of gastric intestinal metaplasia, diagnosed histologically by the presence of goblet cells and Paneth cells. Gastric intestinal metaplasia is believed to an important precursor to the development of gastric cancer. The prevalence of gastric metaplasia varies dramatically worldwide, ranging from 3% to 5% in the United States and Northern European countries to over 20% in East Asia and South America. In the United States, the prevalence is higher among Latinx, Black, and American Indian persons. The estimated risk of developing gastric cancer with intestinal metaplasia is 1.6% within 10 years. Population-based screening for intestinal metaplasia and early gastric cancer is not endorsed by professional guidelines in regions with low gastric cancer incidence but is practiced in high-incidence regions.

In patients undergoing endoscopy for other indications in whom gastric biopsies are obtained, gastric intestinal metaplasia may be identified incidentally. Testing for *H pylori* is recommended, and if present, followed by eradication, which is associated with a 46% reduction in risk of gastric cancer. Routine surveillance in patients with gastric dysplasia for cancer is not recommended by professional guidelines but may be considered in higher risk individuals (eg, family history of gastric cancer).

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Gawron AJ et al. AGA technical review on gastric intestinal metaplasia—natural history and clinical outcomes. Gastroenterology. 2020;158:705. [PMID: 31816300]

Shah SC et al. Surveillance of gastric intestinal metaplasia. Am J Gastroenterol. 2020;115:641. [PMID: 32058339]

A. *Helicobacter pylori* Gastritis

H pylori is a spiral gram-negative rod that resides beneath the gastric mucous layer adjacent to gastric epithelial cells. Although not invasive, it causes gastric mucosal inflammation with PMNs and lymphocytes.

In developed countries, the prevalence of *H pylori* is rapidly declining. In the United States, the prevalence rises from less than 10% in non-immigrants under age 30 years

to over 50% in those over age 60 years. The prevalence is higher in non-Whites and immigrants from developing countries and is correlated inversely with socioeconomic status. Transmission is from person to person, mainly during infancy and childhood; however, the mode of transmission is unknown.

Acute infection with *H pylori* may cause a transient clinical illness characterized by nausea and abdominal pain that may last for several days and is associated with acute histologic gastritis with PMNs. After these symptoms resolve, the majority progress to chronic infection with chronic, diffuse mucosal inflammation (gastritis) characterized by PMNs and lymphocytes. Most persons are asymptomatic and suffer no sequelae. Many patients have inflammation that predominates in the gastric antrum but spares the gastric body (where acid is secreted). People with this phenotype tend to have increased gastrin; increased acid production; and increased risk of developing peptic ulcers, especially duodenal ulcers. Over time, inflammation may become more diffuse, involving the gastric body. In some patients, this may lead to destruction of acid-secreting glands with resultant mucosal atrophy, decreased acid secretion, and intestinal metaplasia. This phenotype is associated with an increased risk of gastric ulcers and gastric cancer. Chronic *H pylori* gastritis leads to the development of duodenal or gastric ulcers in up to 10%, gastric cancer in 0.1–3%, and low-grade B cell gastric lymphoma (mucosa-associated lymphoid tissue lymphoma; MALToma) in less than 0.01%. *H pylori* is estimated to account for 80–89% of non-cardia gastric cancers.

Eradication of *H pylori* may be achieved with antibiotics in over 85% of patients and leads to resolution of the chronic gastritis (see Table 15–10). Testing for *H pylori* is indicated for patients with either active or a past history of documented peptic ulcer disease, gastric metaplasia (see above), gastric MALToma, or a personal or family history of gastric carcinoma. Testing and empiric treatment are cost-effective in young patients (less than 60 years of age) with uncomplicated dyspepsia prior to further medical evaluation. Testing for and treating *H pylori* in patients with functional dyspepsia is generally recommended (see Dyspepsia, above). In addition, to reduce the risk of ulcer-related bleeding, testing for (and, if positive, treating) *H pylori* infection is recommended in patients taking low-dose aspirin or NSAIDs long-term. Some groups recommend population-based screening of all asymptomatic persons in regions in which there is a high prevalence of *H pylori* and gastric cancer (such as Japan, Korea, and China) to reduce the incidence of gastric cancer. Population-based screening of asymptomatic individuals is not recommended in western countries, in which the incidence of gastric cancer is low, but should be considered in immigrants from high-prevalence regions.

1. Noninvasive testing for *H pylori*—Although serologic tests are easily obtained and widely available, clinical guidelines no longer endorse their use for testing for *H pylori* infection. Laboratory-based quantitative serologic ELISA tests have an overall accuracy of only 80%. By contrast, the fecal antigen immunoassay and [^{13}C] urea breath test have excellent sensitivity and specificity (greater than 90–95%). Although more expensive and cumbersome to perform, these tests of active infection are more cost-effective in most clinical settings because they reduce unnecessary treatment for patients without active infection.

Recent PPIs or antibiotics significantly reduce the sensitivity of urea breath tests and fecal antigen assays. Prior to testing, PPIs should be discontinued for 14 days and antibiotics for at least 28 days.

2. Endoscopic testing for *H pylori*—When upper endoscopy is performed in patients with symptoms suggestive of upper GI disease (dyspepsia, dysphagia, vomiting, weight loss, GI bleeding), gastric biopsy specimens can be obtained for histology and detection of *H pylori* with a sensitivity and specificity of greater than 95%. Molecular-based testing of biopsy specimens for antibiotic susceptibility is commercially available but not yet in widespread clinical use.

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B. Pernicious Anemia Gastritis

Pernicious anemia gastritis is a rare autoimmune disorder involving the fundic glands with resultant achlorhydria, decreased intrinsic factor secretion, and vitamin B_{12} malabsorption. Of patients with B_{12} deficiency, a small number have pernicious anemia. Most patients have malabsorption secondary to chronic *H pylori* infection that results in atrophic gastritis, small intestine bacterial overgrowth, or dietary insufficiency. Fundic histology in pernicious anemia is characterized by severe gland atrophy and intestinal metaplasia caused by autoimmune destruction of the gastric fundic mucosa. Anti-intrinsic factor antibodies are present in 70% of patients. Achlorhydria leads to pronounced hypergastrinemia (greater than 1000 pg/mL) due to loss of acid inhibition of gastrin G cells. Hypergastrinemia may induce hyperplasia of gastric enterochromaffin-like cells that may lead to the development of small, multicentric carcinoid tumors in 5% of patients. Metastatic spread is uncommon in lesions smaller than 2 cm. The risk of gastric adenocarcinoma is increased threefold, with a prevalence of 1–3%. Endoscopy with biopsy is indicated in patients with pernicious anemia at the time of diagnosis. Endoscopic surveillance for dysplasia or cancer is not recommended. Pernicious anemia is discussed in detail in Chapter 13.

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Table 15–10. Treatment options for peptic ulcer disease.

Active *Helicobacter pylori*–associated ulcer

1. Treat with anti–*H pylori* regimen for 14 days. Best empiric treatment options:

Standard Bismuth Quadruple Therapy

- PPI orally twice daily[1,2]
- Bismuth subsalicylate 262 mg two tablets orally four times daily or bismuth subcitrate 120–400 mg orally four times daily
- Tetracycline 500 mg orally four times daily
- Metronidazole 500 mg three times daily

OR

- PPI orally twice daily[1]
- Bismuth subcitrate potassium 140 mg/metronidazole 125 mg/tetracycline 125 mg (Pylera) three capsules orally four times daily[3]

Rifabutin-Based Triple Therapy (Talicia)—four capsules, each capsule contains omeprazole 10 mg/rifabutin 12.5 mg/amoxicillin 250 mg, orally every 8 hours, thus total dosages are

- Omeprazole 40 mg orally every 8 hours
- Rifabutin 50 mg orally every 8 hours
- Amoxicillin 1000 mg orally every 8 hours

Standard Triple Therapy (No longer recommended except in locales where clarithromycin resistance is < 15%)

- PPI orally twice daily
- Clarithromycin 500 mg orally twice daily
- Amoxicillin 1 g orally twice daily (or, if penicillin allergic, metronidazole 500 mg orally twice daily)

2. After completion of course of *H pylori* eradication therapy, continue treatment with PPI[1] once daily for 4–6 weeks if ulcer is large (> 1 cm) or complicated.
3. Confirm successful eradication of *H pylori* with urea breath test, fecal antigen test, or endoscopy with biopsy at least 4 weeks after completion of antibiotic treatment and 2 weeks after completion of PPI treatment.

Active ulcer not attributable to *H pylori*

Consider other causes: NSAIDs, Zollinger-Ellison syndrome, gastric malignancy. Treatment options:

- PPIs[1]:
  Uncomplicated duodenal ulcer: treat for 4 weeks
  Uncomplicated gastric ulcer: treat for 8 weeks
- H_2-receptor antagonists:
  Uncomplicated duodenal ulcer: cimetidine 800 mg, nizatidine 300 mg, famotidine 40 mg, orally once daily at bedtime for 6 weeks
  Uncomplicated gastric ulcer: cimetidine 400 mg, nizatidine 150 mg, famotidine 20 mg, orally twice daily for 8 weeks
  Complicated ulcers: PPIs[1] are the preferred drugs

Prevention of ulcer relapse

1. NSAID-induced ulcer: prophylactic therapy for high-risk patients (prior ulcer disease or ulcer complications, use of corticosteroids or anticoagulants, age > 60 years, serious comorbid illnesses). Treatment options:
   - PPI once daily
   - Celecoxib (contraindicated in patients with increased risk of CVD)
   - Misoprostol 200 mcg orally 4 times daily
2. Long-term "maintenance" therapy indicated in patients with recurrent ulcers who either are *H pylori*–negative or who have failed attempts at eradication therapy: once-daily oral PPI[1]

[1]Oral PPIs: omeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, dexlansoprazole 30–60 mg, pantoprazole 40 mg, esomeprazole 40 mg. PPIs are administered 30 minutes before meals.
[2]Preferred regimen in regions with high clarithromycin resistance or in patients who have previously received a macrolide antibiotic or are penicillin allergic. Effective against metronidazole-resistant organisms.
[3]Pylera is an FDA-approved formulation containing bismuth subcitrate 140 mg/tetracycline 125 mg/metronidazole 125 mg per capsule. Packaged for 10-day course; however, 14-day treatment recommended.
[4]Talicia is an FDA approved combination formulation, with each capsule containing omeprazole 10 mg/rifabutin 12.5 mg/amoxicillin 250 mg. Talicia is administered as four capsules orally every 8 hours, thus the dosage is omeprazole 40 mg/rifabutin 50 mg/amoxicillin 1000 mg orally every 8 hours for 14 days.

3. Specific Types of Gastritis

Infections

Acute bacterial infection of the gastric submucosa and muscularis with a variety of aerobic or anaerobic organisms produces a rare, rapidly progressive, life-threatening condition known as phlegmonous or necrotizing gastritis, which requires broad-spectrum antibiotic therapy and, in many cases, emergency gastric resection. Viral infection with CMV is seen in patients with AIDS and after bone marrow or solid organ transplantation. Endoscopic findings include thickened gastric folds and ulcerations. Fungal infection with mucormycosis and *Candida* may occur in immunocompromised and diabetic patients. Larvae of *Anisakis marina* ingested in raw fish or sushi may become embedded in the gastric mucosa, producing severe abdominal pain. Pain persists for several days until the larvae die. Endoscopic removal of the larvae provides rapid symptomatic relief.

PEPTIC ULCER DISEASE

ESSENTIALS OF DIAGNOSIS

- History of dyspepsia present in 80–90% of patients with variable relationship to meals.
- Ulcer symptoms characterized by rhythmicity and periodicity.
- Ulcer complications present without antecedent symptoms in 10–20% of patients.
- Most NSAID-induced ulcers are asymptomatic.
- Upper endoscopy with gastric biopsy for *H pylori* is the diagnostic procedure of choice in most patients.
- Gastric ulcer biopsy or documentation of complete healing necessary to exclude gastric malignancy.

General Considerations

Peptic ulcer is a break in the gastric or duodenal mucosa that arises when the normal mucosal defensive factors are impaired or are overwhelmed by aggressive luminal factors such as acid and pepsin. In the United States, there are about 500,000 new cases per year of peptic ulcer and 4 million ulcer recurrences; the lifetime prevalence of ulcers in the adult population is approximately 10%. Ulcers occur either in the duodenum, where over 95% are in the bulb or pyloric channel, or in the stomach, where benign ulcers are located most commonly in the antrum (60%) or at the junction of the antrum and body on the lesser curvature (25%).

Although ulcers can occur in any age group, duodenal ulcers most commonly occur in patients between the ages of 30 and 55 years, whereas gastric ulcers are more common in patients between the ages of 55 and 70 years. The incidence of duodenal ulcer disease has been declining dramatically for the past 30 years (due to the eradication of *H pylori*), but the incidence of gastric ulcers has not been declining (due to the widespread use of NSAIDs and low-dose aspirin).

Etiology

There are two major causes of peptic ulcer disease: NSAIDs and chronic *H pylori* infection. Evidence of *H pylori* infection or NSAID ingestion should be sought in all patients with peptic ulcer. Alcohol, dietary factors, and stress do not appear to cause ulcer disease. Less than 5–10% of ulcers are caused by other conditions, including acid hypersecretory states (such as Zollinger-Ellison syndrome or systemic mastocytosis), CMV (especially in transplant recipients), Crohn disease, lymphoma, medications (eg, alendronate), or chronic medical illness (cirrhosis or CKD), or are idiopathic.

A. *H pylori*–Associated Ulcers

H pylori infection with associated gastritis appears to be a necessary cofactor for the majority of duodenal and gastric ulcers not associated with NSAIDs. Ulcer disease will develop in an estimated 10% of infected patients. The prevalence of *H pylori* infection in duodenal ulcer patients is 70–90%. The association with gastric ulcers is lower, but *H pylori* is found in most patients in whom NSAIDs cannot be implicated.

The natural history of *H pylori*–associated peptic ulcer disease is well defined. In the absence of specific antibiotic treatment to eradicate the organism, 85% of patients will have an endoscopically visible recurrence within 1 year. Half of these will be symptomatic. After successful eradication of *H pylori* with antibiotics, ulcer recurrence rates are reduced dramatically to 5–20% at 1 year. Most of these ulcer recurrences are due to NSAID use or, rarely, reinfection with *H pylori.*

B. NSAID-Induced Ulcers

There is a 10–20% prevalence of gastric ulcers and a 2–5% prevalence of duodenal ulcers in long-term NSAID users. Approximately 2–5%/year of long-term NSAID users will have an ulcer that causes clinically significant dyspepsia or a serious complication. The incidence of serious GI complications (hospitalization, bleeding, perforation) is 0.2–1.9%/year. Meta-analyses of clinical trials detected an increased risk of upper GI bleeding in patients taking low-dose aspirin (1 of 1000), coxibs (2 of 1000), and nsNSAIDs (4–6 of 1000). The risk of NSAID complications is greater within the first 3 months of therapy and in patients who are older than 60 years; who have a prior history of ulcer disease; or who take NSAIDs in combination with aspirin, corticosteroids, or anticoagulants.

Traditional nsNSAIDs inhibit prostaglandins through reversible inhibition of both COX-1 and COX-2 enzymes. Aspirin causes irreversible inhibition of COX-1 and COX-2 as well as of platelet aggregation. Coxibs (or selective NSAIDs) preferentially inhibit COX-2—the principal enzyme involved in prostaglandin production at sites of inflammation—while providing relative sparing of COX-1, the principal enzyme involved with mucosal cytoprotection in the stomach and duodenum. Celecoxib is the only coxib currently available in the United States, although other older NSAIDs (etodolac, meloxicam) may have similar COX-2/COX-1 selectivity.

Coxibs decrease the incidence of endoscopically visible ulcers by approximately 75% compared with nsNSAIDs. Of greater clinical importance, the risk of significant clinical events (obstruction, perforation, bleeding) is reduced by up to 50% in patients taking coxibs versus nsNSAIDs. However, a twofold increase in the incidence in cardiovascular complications (MI, cerebrovascular infarction, and death) has been detected in patients taking coxibs compared with placebo, prompting the voluntary withdrawal of two highly selective coxibs (rofecoxib and valdecoxib) from the market by the manufacturers. A review by an FDA panel suggested that all NSAIDs (other than aspirin and, possibly, naproxen) may be associated with an increased risk of cardiovascular complications, but concluded that celecoxib, which has less COX-2 selectivity than rofecoxib and valdecoxib, does not have higher risk than other nsNSAIDs when used in currently recommended

doses (200 mg/day). In 2016, a large, randomized, noninferiority trial comparing ibuprofen, naproxen, and celecoxib in arthritis patients with increased cardiovascular risk found no difference in cardiovascular safety between the three drugs over 3 years. However, celecoxib was associated with significantly fewer serious GI events than both naproxen (hazard ratio 0.71) and ibuprofen (hazard ratio 0.65).

Use of even low-dose aspirin (81–325 mg/day) leads to a twofold increased risk of GI bleeding complications. In population studies, GI bleeding occurs in 1.2% of patients each year. Patients with a prior history of peptic ulcers or GI bleeding have a markedly increased risk of complications on low-dose aspirin. It should be noted that low-dose aspirin in combination with NSAIDs or coxibs increases the risk of ulcer complications by up to tenfold compared with NSAIDs or low-dose aspirin alone. Dual antiplatelet therapy with aspirin and a thienopyridine (eg, clopidogrel) incurs a twofold to threefold increased risk of bleeding compared with aspirin alone.

H pylori infection increases the risk of ulcer disease and complications over threefold in patients taking NSAIDs or low-dose aspirin. It is hypothesized that NSAID initiation may potentiate or aggravate ulcer disease in susceptible infected individuals.

Clinical Findings

A. Symptoms and Signs

Epigastric pain (dyspepsia), the hallmark of peptic ulcer disease, is present in 80–90% of patients. However, this complaint is not sensitive or specific enough to serve as a reliable diagnostic criterion for peptic ulcer disease. The clinical history cannot accurately distinguish duodenal from gastric ulcers. Less than 25% of patients with dyspepsia have ulcer disease at endoscopy. Twenty percent of patients with ulcer complications such as bleeding have no antecedent symptoms ("silent ulcers"). Nearly 60% of patients with NSAID-related ulcer complications do not have prior symptoms.

Pain is typically well localized to the epigastrium and not severe. It is described as gnawing, dull, aching, or "hunger-like." Approximately 50% of patients report relief of pain with food or antacids (especially those with duodenal ulcers) and a recurrence of pain 2–4 hours later. However, many patients deny any relationship to meals or report worsening of pain. Two-thirds of duodenal ulcers and one-third of gastric ulcers cause nocturnal pain that awakens the patient. A change from a patient's typical rhythmic discomfort to constant or radiating pain may reflect ulcer penetration or perforation. Most patients have symptomatic periods lasting up to several weeks with intervals of months to years in which they are pain free (periodicity).

Nausea and anorexia may occur with gastric ulcers. Significant vomiting and weight loss are unusual with uncomplicated ulcer disease and suggest gastric outlet obstruction or gastric malignancy.

The physical examination is often normal in uncomplicated peptic ulcer disease. Mild, localized epigastric tenderness to deep palpation may be present. FOBT or FIT is positive in one-third of patients.

B. Laboratory Findings

Laboratory tests are normal in uncomplicated peptic ulcer disease but are ordered to exclude ulcer complications or confounding disease entities. Anemia may occur with acute blood loss from a bleeding ulcer or less commonly from chronic blood loss. Leukocytosis suggests ulcer penetration or perforation. An elevated serum amylase in a patient with severe epigastric pain suggests ulcer penetration into the pancreas. A fasting serum gastrin level to screen for Zollinger-Ellison syndrome is obtained in some patients.

C. Endoscopy

Upper endoscopy is the procedure of choice for the diagnosis of duodenal and gastric ulcers. Duodenal ulcers are virtually never malignant and do not require biopsy. Three to 5 percent of benign-appearing gastric ulcers prove to be malignant. Hence, biopsies of the ulcer margin are almost always performed. Provided that the gastric ulcer appears benign to the endoscopist and adequate biopsy specimens reveal no evidence of cancer, dysplasia, or atypia, the patient may be monitored without further endoscopy. If these conditions are not fulfilled, follow-up endoscopy should be performed 12 weeks after the start of therapy to document complete healing; nonhealing ulcers are suspicious for malignancy.

D. Imaging

Abdominal CT imaging is obtained in patients with suspected complications of peptic ulcer disease (perforation, penetration, or obstruction). Barium upper GI series is no longer recommended.

E. Testing for *H pylori*

In patients in whom an ulcer is diagnosed by endoscopy, gastric mucosal biopsies should be obtained for histologic evaluation. Noninvasive assessment for *H pylori* with fecal antigen assay or urea breath testing may be done in patients with a history of peptic ulcer disease to diagnose active infection or in patients following its treatment to confirm successful eradication. Both tests have a sensitivity and specificity of 92–95%. PPIs may cause false-negative urea breath tests and fecal antigen tests and should be withheld for at least 14 days before testing. Because of its lower sensitivity (85%) and specificity (79%), serologic testing should not be performed unless fecal antigen testing or urea breath testing is unavailable.

Differential Diagnosis

Peptic ulcer disease must be distinguished from other causes of epigastric distress (dyspepsia). Over 50% of patients with dyspepsia have no obvious organic explanation for their symptoms and are classified as having functional dyspepsia (see sections above on Dyspepsia and Functional Dyspepsia). Atypical gastroesophageal reflux may be manifested by epigastric symptoms. Biliary tract disease is characterized by discrete, intermittent episodes of pain that should not be confused with other causes of

dyspepsia. Severe epigastric pain is atypical for peptic ulcer disease unless complicated by a perforation or penetration. Other causes include acute pancreatitis, acute cholecystitis or choledocholithiasis, esophageal rupture, gastric volvulus, gastric or intestinal ischemia, and ruptured aortic aneurysm.

Pharmacologic Agents

Agents that enhance the healing of peptic ulcers may be divided into three categories: (1) acid-antisecretory agents, (2) mucosal protective agents, and (3) agents that promote healing through eradication of *H pylori*.

A. Acid-Antisecretory Agents

1. PPIs—PPIs covalently bind the acid-secreting enzyme H^+-K^+-ATPase, or "proton pump," permanently inactivating it.

There are six oral PPIs currently available: omeprazole, rabeprazole, esomeprazole, lansoprazole, dexlansoprazole, and pantoprazole. Despite minor differences in their pharmacology, they are equally efficacious in the treatment of peptic ulcer disease. Treatment with oral PPIs results in over 90% healing of duodenal ulcers after 4 weeks and 90% of gastric ulcers after 8 weeks when given once daily (30 minutes before breakfast) at the following recommended doses: omeprazole, 20–40 mg; esomeprazole, 40 mg; rabeprazole, 20 mg; lansoprazole, 30 mg; dexlansoprazole, 30–60 mg; and pantoprazole, 40 mg. Compared with H_2-receptor antagonists, PPIs provide faster pain relief and more rapid ulcer healing.

The PPIs are remarkably safe for short-term therapy. (For potential long-term risks, see Gastroesophageal Reflux Disease.) Long-term use may lead to increased risk of enteric infections (including *C difficile*) and micronutrient deficiencies (vitamin B_{12}, iron, magnesium, and possibly calcium). Observational studies report an association with a number of adverse events, including interstitial nephritis, pneumonia, bone fracture, MI, and dementia, but these have not been confirmed in large prospective studies. Nonetheless, long-term PPI therapy should be prescribed only for patients with appropriate indications. Serum gastrin levels rise significantly in 3% of patients receiving long-term therapy but return to normal limits within 2 weeks after discontinuation.

2. H_2-receptor antagonists—Although H_2-receptor antagonists are effective in the treatment of peptic ulcer disease, PPIs are now the preferred agents because of their ease of use and superior efficacy. Three H_2-receptor antagonists are available: cimetidine, famotidine, and nizatidine. For uncomplicated peptic ulcers, H_2-receptor antagonists may be administered once daily at bedtime as follows: nizatidine 300 mg, famotidine 40 mg, and cimetidine 800 mg. Duodenal and gastric ulcer healing rates of 85–90% are obtained within 6 weeks and 8 weeks, respectively. NOTE: Ranitidine has now been withdrawn from the US market by the FDA after an ongoing investigation showed that, when stored at higher-than-normal temperatures, it could contain an increased and unsafe quantity of N-nitrosodimethylamine (NDMA), a probable human carcinogen.

B. Agents Enhancing Mucosal Defenses

Bismuth sucralfate, misoprostol, and antacids all have been shown to promote ulcer healing through the enhancement of mucosal defensive mechanisms. Given the greater efficacy and safety of antisecretory agents and better compliance of patients, these agents are no longer used as first-line therapy for active ulcers in most clinical settings.

C. *H pylori* Eradication Therapy

Eradication of *H pylori* has proved difficult. Combination regimens that use two or three antibiotics with a PPI or bismuth are required to achieve adequate rates of eradication and to reduce the number of failures due to antibiotic resistance. In the United States, up to 50% of strains are resistant to metronidazole and 10–20% are resistant to clarithromycin. Recommended regimens are listed in Table 15–10. Ideally, the optimal regimen would be determined by antibiotic susceptibility testing; however, this requires endoscopic biopsy. In most clinical settings, therapy is chosen empirically. Commercial laboratories now offer culture-based and molecular-based susceptibility testing, which may be helpful for patients who have not responded to an initial empiric course of treatment.

Until recently, in the United States a 14-day course of so-called triple therapy with a PPI, clarithromycin, and either amoxicillin (or metronidazole, if penicillin allergic) was recommended as first-line therapy. However, updated guidelines recommend that triple therapy no longer be used (due to increasing clarithromycin resistance) except in areas with known low-level clarithromycin resistance (less than 15%) or when susceptibility has been confirmed by molecular- or culture-based tests. In most settings, empiric treatment for 14-days is recommended with either a bismuth-based quadruple therapy regimen or a rifabutin-based triple therapy regimen. Both achieve a greater than 85% eradication rate. The bismuth-based quadruple therapy regimen consists of bismuth, tetracycline, a PPI, and metronidazole or tinidazole (Table 15–10). It is effective even for metronidazole-resistant strains. The rifabutin-based regimen contains omeprazole, rifabutin, and amoxicillin (Talicia). Four capsules are taken orally every 8 hours. Rifabutin-resistant strains are rare.

Medical Treatment

Patients should be encouraged to eat balanced meals at regular intervals. There is no justification for bland or restrictive diets. Moderate alcohol intake is not harmful. Smoking retards the rate of ulcer healing and increases the frequency of recurrences and should be prohibited.

A. Treatment of *H pylori*–Associated Ulcers

1. Treatment of active ulcer—The goals of treatment of active *H pylori*–associated ulcers are to relieve dyspeptic symptoms, to promote ulcer healing, and to eradicate *H pylori* infection. Uncomplicated *H pylori*–associated ulcers should be treated for 14 days with one of the PPI-based *H pylori* eradication regimens listed in Table 15–10. At that point, no further antisecretory therapy is needed, provided

the ulcer was small (less than 1 cm) and dyspeptic symptoms have resolved. For patients with large or complicated ulcers, an antisecretory agent should be continued for an additional 2–4 weeks (duodenal ulcer) or 4–6 weeks (gastric ulcer) after completion of the antibiotic regimen to ensure complete ulcer healing. A once-daily oral PPI (as listed in Table 15–10) is recommended. Confirmation of *H pylori* eradication is recommended for all patients more than 4 weeks after completion of antibiotic therapy and more than 2 weeks after discontinuation of the PPI either with noninvasive tests (urea breath test, fecal antigen test) or endoscopy with biopsy for histology.

2. Therapy to prevent recurrence—Successful eradication reduces ulcer recurrences to less than 20% after 1–2 years. The most common cause of recurrence after antibiotic therapy is failure to achieve successful eradication. Once cure has been achieved, reinfection rates are less than 0.5% per year. Although *H pylori* eradication has reduced the need for long-term maintenance antisecretory therapy to prevent ulcer recurrences, there remains a subset of patients who require long-term therapy with a PPI once daily. This subset includes patients with *H pylori*–positive ulcers who have not responded to repeated attempts at eradication therapy, patients with a history of *H pylori*–positive ulcers who have recurrent ulcers despite successful eradication, and patients with idiopathic ulcers (ie, *H pylori*–negative and not taking NSAIDs). In all patients with recurrent ulcers, NSAID usage (unintentional or surreptitious) and hypersecretory states (including gastrinoma) should be excluded.

B. Treatment of NSAID-Induced Ulcers

1. Treatment of active ulcers—In patients with NSAID-induced ulcers, the offending agent should be discontinued whenever possible. Both gastric and duodenal ulcers respond rapidly to therapy with H_2-receptor antagonists or PPIs (Table 15–10) once NSAIDs are eliminated. All patients with NSAID-associated ulcers should undergo testing for *H pylori* infection. Antibiotic eradication therapy should be given if *H pylori* tests are positive.

2. Prevention of NSAID-induced ulcers—Clinicians should carefully weigh the benefits of NSAID therapy with the risks of cardiovascular and GI complications. Ulcer complications occur in up to 2% of all nsNSAID-treated patients per year, but in up to 10–20% per year of patients with multiple risk factors. These include age over 60 years, history of ulcer disease or complications, concurrent use of antiplatelet therapy (low-dose aspirin or clopidogrel, or both), concurrent therapy with anticoagulants or corticosteroids, and serious underlying medical illness. After considering the patient's risk of cardiovascular and GI complications due to NSAID use, the clinician can decide what type of NSAID (nsNSAID vs coxib) is appropriate and what strategies should be used to reduce the risk of such complications. To minimize cardiovascular and GI risks, all NSAIDs should be used at the lowest effective dose and for the shortest time necessary.

a. Test for and treat *H pylori* infection—All patients with a known history of peptic ulcer disease who are treated with NSAIDs or antiplatelet agents (aspirin, clopidogrel) should be tested for *H pylori* infection and treated, if positive. Although *H pylori* eradication may decrease the risk of NSAID-related complications, cotherapy with a PPI is still required in high-risk patients.

b. PPI—Treatment with an oral PPI given once daily (rabeprazole 20 mg, omeprazole 20–40 mg, lansoprazole 30 mg, dexlansoprazole 30–60 mg, or pantoprazole or esomeprazole 40 mg) is effective in the prevention of NSAID-induced gastric and duodenal ulcers and is approved by the FDA for this indication. Among high-risk patients taking nsNSAIDs or coxibs, the incidence of endoscopically visible gastric and duodenal ulcers after 6 months of therapy in patients treated with esomeprazole 20–40 mg/day was 5%, compared with 17% who were given placebo. Nonetheless, PPIs are not fully protective in high-risk patients in preventing NSAID-related complications. In prospective, controlled trials of patients with a prior history of NSAID-related ulcer complications, the incidence of recurrent bleeding was almost 5% after 6 months in patients taking nsNSAIDs and a PPI. In prospective, controlled trials of patients with a prior history of ulcer complications related to low-dose aspirin, the incidence of recurrent ulcer bleeding in patients taking low-dose aspirin alone was approximately 15% per year compared with 0–2% per year in patients taking low-dose aspirin and PPI and 9–14% per year in patients taking clopidogrel. Thus, PPIs are highly effective in preventing complications related to low-dose aspirin, even in high-risk patients. Enteric coating of aspirin may reduce direct topical damage to the stomach but does not reduce its other complications.

c. Recommendations to reduce risk of ulcer complications from nsNSAIDs and coxibs—For patients with a low risk of CVD who have no risk factors for GI complications, an nsNSAID alone may be given. For patients with one or two GI risk factors, a coxib alone or an nsNSAID should be given with a PPI once daily to reduce the risk of GI complications. NSAIDs should be avoided, if possible, in patients with multiple risk factors; if required, however, combination therapy of celecoxib or a partially COX-2 selective nsNSAID (etodolac, meloxicam) with a PPI once daily is recommended.

For patients with an increased risk of cardiovascular complications, it is preferable to avoid NSAIDs, if possible. Almost all patients with increased cardiovascular risk also will be taking antiplatelet therapy with low-dose aspirin or clopidogrel, or both. Because combination therapy with an nsNSAID and antiplatelet therapy increases the risks of GI complications, these patients should all receive cotherapy with a PPI once daily or misoprostol.

d. Recommendations to reduce risk of ulcer complications with use of antiplatelet agents—The risk of significant GI complications in persons taking low-dose aspirin (81–325 mg/day) or clopidogrel, or both, for cardiovascular prophylaxis is 0.5%/year. Aspirin, 81 mg/day, is recommended in most patients because it has a

lower risk of GI complications but equivalent cardiovascular protection compared with higher aspirin doses. Complications are increased with combinations of aspirin and clopidogrel or aspirin and anticoagulants. Clopidogrel does not cause GI ulcers or erosions. However, its antiplatelet activity may promote bleeding from erosions or ulcers caused by low-dose aspirin or *H pylori*. Patients with dyspepsia or prior ulcer disease should be tested for *H pylori* infection and treated, if positive. Patients younger than 60–70 years who have no other risk factors for GI complications may be treated with low-dose aspirin or dual antiplatelet therapy without a PPI. Virtually all other patients who require low-dose aspirin or aspirin plus anticoagulant therapy should receive a PPI once daily.

At the present time, the optimal management of patients who require dual antiplatelet therapy with clopidogrel and aspirin is uncertain. Clopidogrel is a prodrug that is activated by the cytochrome P450 CYP2C19 enzyme. All PPIs inhibit CYP2C19 to varying degrees, with omeprazole having the highest and pantoprazole the least level of inhibition. In vitro and in vivo platelet aggregation studies demonstrate that PPIs (especially omeprazole) may attenuate the antiplatelet effects of clopidogrel, although the clinical importance of this interaction is uncertain. The FDA has issued a warning that patients should avoid using clopidogrel with omeprazole and esomeprazole. A 2010 expert consensus panel concluded that once daily treatment with an oral PPI (pantoprazole 40 mg; rabeprazole 20 mg; lansoprazole or dexlansoprazole 30 mg) may be recommended for patients who have an increased risk of upper GI bleeding (prior history of peptic ulcer disease or GI bleeding; concomitant NSAIDs). For patients with a lower risk of GI bleeding, the risks and benefits of PPIs must be weighed. Pending further recommendations, an acceptable alternative is to treat with an oral H_2-receptor antagonist (famotidine 20 mg, nizatidine 150 mg) twice daily; however, PPIs are more effective in preventing upper GI bleeding. Cimetidine is a CYP2C19 inhibitor and should not be used. An alternative strategy is ticagrelor, an antiplatelet agent approved for use with low-dose aspirin in the treatment of acute coronary syndrome. Like clopidogrel, ticagrelor blocks the platelet ADP p2y12 receptor; however, it does not require hepatic activation, it does not interact with the CYP2C19 enzyme, and its efficacy is not diminished by PPIs.

C. Refractory Ulcers

Ulcers that are truly refractory to medical therapy are now uncommon. Less than 5% of ulcers are unhealed after 8 weeks of once daily therapy with PPIs, and almost all benign ulcers heal with twice-daily therapy. Thus, noncompliance is the most common cause of ulcer nonhealing. NSAID and aspirin use, sometimes surreptitious, are commonly implicated in refractory ulcers and must be stopped. Single or multiple linear gastric ulcers may occur in large hiatal hernias where the stomach slides back and forth through the diaphragmatic hiatus ("Cameron lesions"); this may be a cause of iron deficiency anemia. Other causes of nonhealing ulcers include acid hypersecretion (Zollinger-Ellison syndrome), unrecognized malignancy (adenocarcinoma or lymphoma), medications causing GI ulceration (eg, iron or bisphosphonates), Crohn disease, and unusual infections (*H heilmanii*, CMV, mucormycosis). Fasting serum gastrin levels should be obtained to exclude gastrinoma with acid hypersecretion (Zollinger-Ellison syndrome). Repeat ulcer biopsies are mandatory after 2–3 months of therapy in all nonhealed ulcers to look for malignancy or infection. Patients with persistent nonhealing ulcers are referred for surgical therapy after exclusion of NSAID use and persistent *H pylori* infection.

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COMPLICATIONS OF PEPTIC ULCER DISEASE

1. GI Hemorrhage

ESSENTIALS OF DIAGNOSIS

- "Coffee grounds" emesis, hematemesis, melena, or hematochezia.
- Emergent upper endoscopy is diagnostic and therapeutic.

General Considerations

Approximately 50% of all episodes of upper GI bleeding are due to peptic ulcer. Clinically significant bleeding occurs in 10% of ulcer patients. About 80% of patients stop bleeding spontaneously and generally have an uneventful recovery; the remaining 20% have more severe bleeding. The overall mortality rate for ulcer bleeding is 7%, but it is higher in older patients, in patients with comorbid medical problems, and in patients with hospital-associated bleeding. Mortality is also higher in patients who present with persistent hypotension or shock, bright red blood in the vomitus or nasogastric lavage fluid, or severe coagulopathy.

Clinical Findings

A. Symptoms and Signs

Up to 20% of patients have no antecedent symptoms of pain; this is particularly true of patients receiving NSAIDs. Common presenting signs include melena and hematemesis. Massive upper GI bleeding or rapid GI transit may result in hematochezia rather than melena; this may be misinterpreted as signifying a lower tract bleeding source. Nasogastric lavage that demonstrates "coffee grounds" or

bright red blood confirms an upper tract source. Recovered nasogastric lavage fluid that is negative for blood does not exclude active bleeding from a duodenal ulcer.

B. Laboratory Findings

The hematocrit may fall as a result of bleeding or expansion of the intravascular volume with intravenous fluids. The BUN may rise as a result of absorption of blood nitrogen from the small intestine and prerenal azotemia.

Treatment

A. Medical Therapy

1. Antisecretory agents—Intravenous PPIs should be administered for 3 days in patients with ulcers whose endoscopic appearance suggests a high risk of rebleeding after endoscopic therapy. Intravenous PPIs have been associated with a reduction in rebleeding, transfusions, need for further endoscopic therapy, and surgery in the subset of patients with high-risk ulcers, ie, an ulcer with active bleeding, visible vessel, or adherent clot. After initial successful endoscopic treatment of ulcer hemorrhage, intravenous esomeprazole, pantoprazole, or omeprazole (80 mg bolus injection, followed by 8 mg/hour continuous infusion for 72 hours) reduces the rebleeding rate from approximately 20% to less than 10%; however, intravenous omeprazole is not available in the United States.

High-dose oral PPIs (omeprazole 40 mg twice daily) also appear to be effective in reducing rebleeding but have not been compared with the intravenous regimen. Intravenous H_2-receptor antagonists have not been demonstrated to be of any benefit in the treatment of acute ulcer bleeding.

2. Long-term prevention of rebleeding—Recurrent ulcer bleeding develops within 3 years in one-third of patients if no specific therapy is given. In patients with bleeding ulcers who are *H pylori*–positive, successful eradication effectively prevents recurrent ulcer bleeding in almost all cases. It is therefore recommended that all patients with bleeding ulcers be tested for *H pylori* infection and treated if positive. Four weeks after completion of antibiotic therapy, a urea breath or fecal antigen test for *H pylori* should be administered or endoscopy performed with biopsy and histology for confirmation of successful eradication. In patients in whom *H pylori* persists or the small subset of patients whose ulcers are not associated with NSAIDs or *H pylori*, long-term acid suppression with a once-daily PPI should be prescribed to reduce the likelihood of recurrence of bleeding.

B. Endoscopy

Endoscopy is the preferred diagnostic procedure in almost all cases of upper GI bleeding because of its high diagnostic accuracy, its ability to predict the likelihood of recurrent bleeding, and its availability for therapeutic intervention in high-risk lesions. Endoscopy should be performed within 24 hours in most cases. In cases of severe active bleeding, endoscopy should be performed after patients have been appropriately resuscitated and are hemodynamically stable.

On the basis of clinical and endoscopic criteria, it is possible to predict which patients are at a higher risk of rebleeding and therefore to make more rational use of hospital resources. Nonbleeding ulcers under 2 cm in size with a base that is clean have a less than 5% chance of rebleeding. Most young (under age 60 years), otherwise healthy patients with clean-based ulcers may be safely discharged from the emergency department or hospital after endoscopy. Ulcers that have a flat red or black spot have a less than 10% chance of significant rebleeding. Patients who are hemodynamically stable with these findings should be admitted to a hospital ward for 24–72 hours and may begin immediate oral feedings and antiulcer (or anti–*H pylori*) medication.

By contrast, the risk of rebleeding or continued bleeding in ulcers with a nonbleeding visible vessel is 50%, and with active bleeding, it is 80–90%. Endoscopic therapy with thermocoagulation (bipolar or heater probes) or application of endoscopic clips (akin to a staple) is the standard of care for such lesions because it reduces the risk of rebleeding, the number of transfusions, and the need for subsequent surgery. The optimal treatment of ulcers with a dense clot that adheres despite vigorous washing is controversial; removal of the clot followed by endoscopic treatment of an underlying vessel may be considered in selected high-risk patients. For actively bleeding ulcers, a combination of epinephrine injection followed by thermocoagulation or clip application commonly is used. These techniques achieve successful hemostasis of actively bleeding lesions in 90% of patients. Endoscopic application of a topical hemostatic powder (Hemospray) may provide temporary hemostasis for up to 24 hours in patients with massive bleeding that interferes with effective application of thermocoagulation or endoclip placement. After endoscopic therapy followed by an intravenous PPI, significant rebleeding occurs in less than 10% of cases, of which over 70% can be managed successfully with repeat endoscopic treatment. After endoscopic treatment, patients should remain hospitalized for at least 72 hours, when the risk of rebleeding falls to below 3%.

C. Recurrent Bleeding

Less than 5% of patients have persistent or recurrent bleeding that cannot be controlled with endoscopic techniques. The availability of newer, larger over-the-scope clips has further reduced the risk of persistent bleeding requiring other more aggressive interventions. In a randomized prospective study of patients with recurrent ulcer bleeding after conventional medical and endoscopic therapy, persistent bleeding occurred in 6% of patients treated with over-the-scope clips versus 42.4% treated with further conventional endoscopic modalities. For patients in whom endoscopic therapy is unsuccessful, percutaneous radiologic embolization or surgery should be considered. Overall surgical mortality for emergency ulcer bleeding is less than 6%. The prognosis is poorer for patients over age 60 years, those with serious underlying medical illnesses or CKD, and those who require more than 10 units of blood transfusion.

2. Ulcer Perforation

Perforations develop in less than 5% of ulcer patients, usually from ulcers on the anterior wall of the stomach or duodenum. Perforation results in a chemical peritonitis that causes sudden, severe generalized abdominal pain that prompts most patients to seek immediate attention. Older adults or debilitated patients and those receiving long-term corticosteroid therapy may experience minimal initial symptoms, presenting late with bacterial peritonitis, sepsis, and shock. On physical examination, patients appear ill, with a rigid, quiet abdomen and rebound tenderness. Hypotension develops later after bacterial peritonitis has developed. If hypotension is present early with the onset of pain, other abdominal emergencies should be considered such as a ruptured aortic aneurysm, mesenteric infarction, or acute pancreatitis. Leukocytosis is almost always present. A mildly elevated serum amylase (less than twice normal) is sometimes seen with ulcer perforation. Abdominal CT usually establishes the diagnosis without need for further studies. The absence of free air may lead to a misdiagnosis of pancreatitis, cholecystitis, or appendicitis.

Laparoscopic closure of perforations can be performed in many centers, significantly reducing operative morbidity compared with open laparotomy.

3. Gastric Outlet Obstruction

Gastric outlet obstruction occurs in less than 2% of patients with ulcer disease and is due to edema or cicatricial narrowing of the pylorus or duodenal bulb. With the advent of potent antisecretory therapy with PPIs and the eradication of *H pylori*, obstruction now is less commonly caused by peptic ulcers than by gastric neoplasms or extrinsic duodenal obstruction by intra-abdominal neoplasms. The most common symptoms are early satiety, vomiting, and weight loss. Later, vomiting may develop that typically occurs one to several hours after eating and consists of partially digested food contents. Patients may develop dehydration, metabolic alkalosis, and hypokalemia. On physical examination, a succussion splash may be heard in the epigastrium. In most cases, nasogastric aspiration will result in evacuation of a large amount (greater than 200 mL) of foul-smelling fluid, which establishes the diagnosis. Patients are treated initially with intravenous isotonic saline and KCl to correct fluid and electrolyte disorders, an intravenous PPI, and nasogastric decompression of the stomach. Upper endoscopy is performed after 24–72 hours to define the nature of the obstruction and to exclude gastric neoplasm.

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ZOLLINGER-ELLISON SYNDROME (Gastrinoma)

ESSENTIALS OF DIAGNOSIS

- Peptic ulcer disease; may be severe and atypical.
- Gastric acid hypersecretion.
- Diarrhea common, relieved by nasogastric suction.
- Most cases are sporadic; 25% occur with multiple endocrine neoplasia type 1 (MEN 1).

General Considerations

Zollinger-Ellison syndrome is caused by gastrin-secreting gut neuroendocrine tumors (gastrinomas), which result in hypergastrinemia and acid hypersecretion. Less than 1% of peptic ulcer disease is caused by gastrinomas. Primary gastrinomas may arise in the pancreas (25%), duodenal wall (45%), or lymph nodes (5–15%), and in other locations including unknown primary sites (20%). Approximately 80% arise within the "gastrinoma triangle" bounded by the porta hepatis, the neck of the pancreas, and the third portion of the duodenum. Most gastrinomas are solitary or multifocal nodules that are potentially resectable. Approximately 25% of patients have small multicentric gastrinomas associated with MEN 1 that are more difficult to resect. Over two-thirds of gastrinomas are malignant, and one-third have already metastasized to the liver at initial presentation.

Clinical Findings

A. Symptoms and Signs

Over 90% of patients with Zollinger-Ellison syndrome develop peptic ulcers. In most cases, the symptoms are indistinguishable from other causes of peptic ulcer disease, and therefore, the syndrome may go undetected for years. Ulcers usually are solitary and located in the duodenal bulb, but they may be multiple or occur more distally in the duodenum. Isolated gastric ulcers do not occur. Gastroesophageal reflux symptoms occur often. Diarrhea occurs in one-third of patients, in some cases in the absence of peptic symptoms. Gastric acid hypersecretion can cause direct intestinal mucosal injury and pancreatic enzyme inactivation, resulting in diarrhea, steatorrhea, and weight loss; nasogastric aspiration of stomach acid stops the diarrhea. Screening for Zollinger-Ellison syndrome with fasting gastrin levels should be done in patients with ulcers that are refractory to standard therapies, giant ulcers (larger than 2 cm), ulcers located distal to the duodenal bulb, multiple duodenal ulcers, frequent ulcer recurrences, ulcers associated with diarrhea, ulcers occurring after ulcer surgery, and ulcers with complications. Ulcer patients with hypercalcemia or family histories of ulcers (suggesting MEN 1) should also be screened. Finally, patients with peptic ulcers who are *H pylori* negative and who are not taking NSAIDs should be screened.

B. Laboratory Findings

The most sensitive and specific method for identifying Zollinger-Ellison syndrome is demonstration of an increased fasting serum gastrin concentration (greater than 150 pg/mL [150 ng/L]). If possible, levels should be obtained with patients not taking H_2-receptor antagonists for 24 hours or PPIs for 6 days; however, withdrawal of the PPI may result in marked gastric hypersecretion with serious consequences and patients should be closely monitored. The median gastrin level is 500–700 pg/mL (500–700 ng/L), and 60% of patients have levels less than 1000 pg/mL (1000 ng/L). Hypochlorhydria with increased gastric pH is a much more common cause of hypergastrinemia than is gastrinoma. Therefore, a measurement of gastric pH (and, where available, a gastric secretory study) is performed in patients with fasting hypergastrinemia. Most patients have a basal acid output of over 15 mEq/hour. A gastric pH of greater than 3.0 implies hypochlorhydria and excludes gastrinoma. In a patient with a serum gastrin level of greater than 1000 pg/mL (1000 ng/L) and gastric pH < 2, the diagnosis of Zollinger-Ellison syndrome is established. With lower gastrin levels (150–1000 pg/mL [150–1000 ng/L]) and acid secretion, a secretin stimulation test may be performed to distinguish Zollinger-Ellison syndrome from other causes of hypergastrinemia. Intravenous secretin (2 U/kg) produces a rise in serum gastrin of over 200 pg/mL (200 ng/L) within 2–30 minutes in 85% of patients with gastrinoma. An elevated serum calcium suggests hyperparathyroidism and MEN 1 syndrome. In all patients with Zollinger-Ellison syndrome, serum parathyroid hormone (PTH), prolactin, LH-FSH, and growth hormone (GH) levels should be obtained to exclude MEN 1.

C. Imaging

Imaging studies are obtained in an attempt to determine whether there is metastatic disease and, if not, to identify the site of the primary tumor. CT and MRI scans are commonly obtained first to look for large hepatic metastases and primary lesions, but they have low sensitivity for small lesions. Gastrinomas express somatostatin receptors that bind radiolabeled octreotide and Gallium-68 dotatate. Full body ^{68}Ga-PET scans (preferably combined with CT) have a sensitivity of greater than 90% for detection of primary tumor in the pancreas, duodenum, and lymph nodes as well as for detection of metastatic disease in liver and bone. Where available, ^{68}Ga-PET/CT has supplanted somatostatin receptor scintigraphy with single PET. In patients with negative ^{68}Ga-PET/CT or somatostatin receptor scintigraphy, endoscopic ultrasonography may be useful to detect small gastrinomas in the duodenal wall, pancreas, or peripancreatic lymph nodes.

Differential Diagnosis

Gastrinomas are one of several gut neuroendocrine tumors that have similar histopathologic features and arise either from the gut or pancreas. These include carcinoid, insulinoma, VIPoma, glucagonoma, and somatostatinoma. These tumors usually are differentiated by the gut peptides that they secrete; however, poorly differentiated neuroendocrine tumors may not secrete any hormones. Patients may present with symptoms caused by tumor metastases (jaundice, hepatomegaly) rather than functional symptoms. Once a diagnosis of a neuroendocrine tumor is established from the liver biopsy, the specific type of tumor can subsequently be determined. Both carcinoid and gastrinoma tumors may be detected incidentally during endoscopy after biopsy of a submucosal nodule and must be distinguished by subsequent studies.

Hypergastrinemia due to gastrinoma must be distinguished from other causes of hypergastrinemia. Atrophic gastritis with decreased acid secretion is detected by gastric secretory analysis. Other conditions associated with hypergastrinemia (eg, gastric outlet obstruction, vagotomy, CKD) are associated with a negative secretin stimulation test.

Treatment

A. Metastatic Disease

The most important predictor of survival is the presence of metastases (liver or bone). In patients with multiple metastases, initial therapy should be directed at controlling hypersecretion. Oral PPIs (omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole, dexlansoprazole) are given at a dose of 40–120 mg/day, titrated to achieve a basal acid output of less than 10 mEq/hour. At this level, there is complete symptomatic relief and ulcer healing. Systemic therapies include long-acting somatostatin analogs (Octreotide LAR, lanreotide), tyrosine kinase inhibitors, and peptide receptor radionucleotide therapy. Owing to the slow growth of these tumors, 30% of patients with hepatic metastases have a survival of 10 years.

B. Localized Disease

Cure can be achieved only if the gastrinoma can be resected before hepatic metastatic spread has occurred. Lymph node metastases do not adversely affect prognosis. Laparotomy should be considered in all patients in whom preoperative studies fail to demonstrate hepatic or other distant metastases. A combination of preoperative studies, duodenotomy with careful duodenal inspection, and intraoperative palpation and sonography allows successful localization and resection in the majority of cases. The 15-year survival of patients who do not have liver metastases at initial presentation is over 95%. Surgery usually is not recommended in patients with MEN 1 due to the presence of multifocal tumors and long-term survival in the absence of surgery in most patients.

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DISEASES OF THE SMALL INTESTINE

MALABSORPTION

The term "malabsorption" denotes disorders in which there is a disruption of digestion and nutrient absorption. The clinical and laboratory manifestations of malabsorption are summarized in Table 15–11.

Table 15–11. Clinical manifestations and laboratory findings in malabsorption of various nutrients.

Manifestations	Laboratory Findings	Malabsorbed Nutrients
Steatorrhea (bulky, light-colored stools)	Increased fecal fat; decreased serum cholesterol; decreased serum carotene, vitamin A, vitamin D	Triglycerides, fatty acids, phospholipids, cholesterol. Fat-soluble vitamins: A, D, E, K
Diarrhea (increased fecal water)	Increased stool volume and weight; increased fecal fat; increased stool osmolality gap	Fats, carbohydrates
Weight loss; muscle wasting	Increased fecal fat; decreased carbohydrate (D-xylose) absorption	Fat, protein, carbohydrates
Microcytic anemia	Low serum iron	Iron
Macrocytic anemia	Decreased serum vitamin B_{12} or RBC folate	Vitamin B_{12} or folic acid
Paresthesia; tetany; positive Trousseau and Chvostek signs	Decreased serum calcium or magnesium	Calcium, vitamin D, magnesium
Bone pain; pathologic fractures; skeletal deformities	Osteopenia on radiograph; osteoporosis (adults); osteomalacia (children)	Calcium, vitamin D
Bleeding tendency (ecchymoses, epistaxis)	Prolonged prothrombin time or INR	Vitamin K
Edema	Decreased serum total protein and albumin; increased fecal loss of alpha-1-antitrypsin	Protein
Milk intolerance (cramps, bloating, diarrhea)	Abnormal lactose tolerance test	Lactose

1. Celiac Disease

ESSENTIALS OF DIAGNOSIS

- *Typical symptoms*: weight loss, chronic diarrhea, abdominal distention, growth retardation.
- *Atypical symptoms*: dermatitis herpetiformis, iron deficiency anemia, osteoporosis.
- Abnormal serologic test results.
- Abnormal small bowel biopsy.
- Clinical improvement on gluten-free diet.

General Considerations

Celiac disease (also called sprue, celiac sprue, and gluten enteropathy) is a permanent dietary disorder caused by an immunologic response to gluten, a storage protein found in certain grains, that results in diffuse damage to the proximal small intestinal mucosa with malabsorption of nutrients. Although symptoms may manifest between 6 months and 24 months of age after the introduction of weaning foods, most cases present in childhood or adulthood. Population screening with serologic tests suggests that the global prevalence of this disease is 1.4%. In North America, the prevalence of biopsy-confirmed disease is 0.5%. Although the precise pathogenesis is unclear, celiac disease arises in a small subset of genetically susceptible (-DQ2 or -DQ8) individuals when dietary gluten stimulates an inappropriate immunologic response.

Clinical Findings

The most important step in diagnosing celiac disease is to consider the diagnosis. Because of its protean manifestations, celiac disease is underdiagnosed in the adult population.

A. Symptoms and Signs

The GI symptoms and signs of celiac disease depend on the length of small intestine involved and the patient's age when the disease presents. "Classic" symptoms of malabsorption, including diarrhea, steatorrhea, weight loss, abdominal distention, weakness, muscle wasting, or growth retardation, more commonly present in infants (younger than 2 years). Older children and adults are less likely to manifest signs of serious malabsorption. They may report chronic diarrhea, dyspepsia, or flatulence due to colonic bacterial digestion of malabsorbed nutrients, but the severity of weight loss is variable. Many adults have minimal or no GI symptoms but present with extraintestinal "atypical" manifestations, including fatigue, depression, iron deficiency anemia, osteoporosis, short stature, delayed puberty, amenorrhea, or reduced fertility. Approximately 40% of patients with positive serologic tests consistent with disease have no symptoms of disease; the natural history of these patients with "silent" disease is unclear.

Physical examination may be normal in mild cases or may reveal signs of malabsorption such as loss of muscle mass or subcutaneous fat, pallor due to anemia, easy bruising due to vitamin K deficiency, hyperkeratosis due to vitamin A deficiency, bone pain due to osteomalacia, or neurologic signs (peripheral neuropathy, ataxia) due to vitamin B_{12} or vitamin E deficiency (Table 15–11). Abdominal examination may reveal distention with hyperactive bowel sounds.

Dermatitis herpetiformis is regarded as a cutaneous variant of celiac disease. It is a characteristic skin rash consisting of pruritic papulovesicles over the extensor surfaces of the extremities and over the trunk, scalp, and neck.

Dermatitis herpetiformis occurs in less than 10% of patients with celiac disease; however, almost all patients who present with dermatitis herpetiformis have evidence of celiac disease on intestinal mucosal biopsy, though it may not be clinically evident.

B. Laboratory Findings

1. Routine laboratory tests—Depending on the severity of illness and the extent of intestinal involvement, nonspecific laboratory abnormalities may be present that may raise the suspicion of malabsorption and celiac disease (Table 15–11). Limited proximal involvement may result only in microcytic anemia due to iron deficiency. Up to 3% of adults with iron deficiency not due to GI blood loss have undiagnosed celiac disease. Megaloblastic anemia may be due to folate or vitamin B_{12} deficiency (due to terminal ileal involvement or associated autoimmune gastritis). Low serum calcium or elevated alkaline phosphatase may reflect impaired calcium or vitamin D absorption with osteomalacia or osteoporosis. Dual-energy x-ray densitometry scanning is recommended for all patients with celiac disease to screen for osteoporosis. Elevations of prothrombin time, or decreased vitamin A or D levels reflect impaired fat-soluble vitamin absorption. A low serum albumin may reflect small intestine protein loss or poor nutrition. Other deficiencies may include zinc and vitamin B_6. Mild elevations of aminotransferases are found in up to 40%.

2. Serologic tests—Serologic tests should be performed in all patients in whom there is a suspicion of celiac disease. Patient self-elimination of gluten before serologic testing may result in false-negative test results. The recommended test is the IgA tissue transglutaminase-2 antibody (IgA anti-tTG2), which has a 98% sensitivity and 98% specificity for the diagnosis of celiac disease. Antigliadin antibodies are not recommended because of their lower sensitivity and specificity. An IgA level should be obtained in patients with a negative IgA TG antibody when celiac disease is strongly suspected because up to 3% of patients with celiac disease have IgA deficiency. In patients with IgA deficiency, tests that measures IgG antibodies to tissue transglutaminase (IgG tTG) or to deamidated gliadin peptides (anti-DGP) have excellent sensitivity and specificity. Levels of all antibodies become undetectable after 3–24 months of dietary gluten withdrawal and may be used to monitor dietary compliance, especially in patients whose symptoms fail to resolve after institution of a gluten-free diet.

C. Mucosal Biopsy

Endoscopic mucosal biopsy of the proximal duodenum (bulb) and distal duodenum is the standard method for confirmation of the diagnosis in patients with a positive serologic test for celiac disease. At endoscopy, atrophy or scalloping of the duodenal folds may be observed. Histology reveals abnormalities ranging from intraepithelial lymphocytosis alone to extensive infiltration of the lamina propria with lymphocytes and plasma cells, hypertrophy of the intestinal crypts, and blunting or complete loss of intestinal villi. In patients in whom celiac disease is first suspected on intestinal biopsies, celiac serologic tests should be obtained to confirm the diagnosis. Partial or complete reversion of these abnormalities occurs within 3–24 months after a patient is placed on a gluten-free diet, but symptom resolution remains incomplete in 30% of patients. If a patient with a compatible biopsy demonstrates prompt clinical improvement on a gluten-free diet and a decrease in serologic markers, a repeat biopsy is unnecessary.

Differential Diagnosis

Many patients with chronic diarrhea or flatulence are erroneously diagnosed as having IBS. Celiac disease must be distinguished from other causes of malabsorption, as outlined above. Severe panmalabsorption of multiple nutrients is almost always caused by mucosal disease. The histologic appearance of celiac disease may resemble other mucosal diseases such as tropical sprue, bacterial overgrowth, cow's milk intolerance, viral gastroenteritis, eosinophilic gastroenteritis, and mucosal damage caused by acid hypersecretion associated with gastrinoma. Documentation of clinical response to gluten withdrawal therefore is essential to the diagnosis.

Over the past decade, there has been a growing proportion (now 10%) of the population reporting symptoms after gluten ingestion who do not have serologic or histologic evidence of celiac disease. This has led to increases in gluten-free offerings from the restaurant and food industry. Foods with gluten often contain a number of other FODMAPs. Blinded clinical trials suggest that self-reported wheat sensitivity is not due to gluten intolerance and that the symptom improvement reported by patients with gluten restriction is due to broader FODMAP elimination.

Treatment

Removal of all gluten (wheat, rye, and barley) from the diet is essential to therapy but strict adherence can be difficult to achieve. Even among patients who report adherence to the gluten-free diet, gluten peptides can be detected in almost 40% of stool and urine specimens over a 4-week period. Although oats appear to be safe for many patients, commercial products may be contaminated with wheat or barley during processing. Because of the pervasive use of gluten products in manufactured foods and additives, in medications, and by restaurants, it is imperative that patients and their families confer with a knowledgeable dietitian to comply satisfactorily with this lifelong diet. Several excellent dietary guides and patient support groups are available. Most patients with celiac disease also have lactose intolerance either temporarily or permanently and should avoid dairy products until the intestinal symptoms have improved on the gluten-free diet. Dietary supplements (folate, iron, zinc, calcium, and vitamins A, B_6, B_{12}, D, and E) should be provided in the initial stages of therapy but usually are not required long-term with a gluten-free diet. Patients with confirmed osteoporosis may require long-term calcium, vitamin D, and bisphosphonate therapy.

Improvement in symptoms should be evident within a few weeks on the gluten-free diet. The most common reason

for treatment failure is incomplete removal of gluten. Intentional or unintentional rechallenge with gluten may trigger acute severe diarrhea with dehydration and electrolyte imbalance and may require TPN and intravenous or oral corticosteroids (prednisone 40 mg or budesonide 9 mg) for 2 or more weeks while a gluten-free diet is reinitiated.

Prognosis & Complications

If appropriately diagnosed and treated, patients with celiac disease have an excellent prognosis. Celiac disease may be associated with other autoimmune disorders, including Addison disease, Graves disease, type 1 diabetes mellitus, myasthenia gravis, systemic sclerosis, Sjögren syndrome, atrophic gastritis, and pancreatic insufficiency. In some patients, celiac disease may evolve and become refractory to the gluten-free diet. The most common cause is intentional or unintentional dietary noncompliance, which may be suggested by positive serologic tests. Celiac disease that is truly refractory to gluten withdrawal occurs in 0.5–1.5% and generally carries a poor prognosis. There are two types of refractory disease, which are distinguished by their intraepithelial lymphocyte phenotype. This diagnosis should be considered in patients previously responsive to the gluten-free diet in whom new weight loss, abdominal pain, and malabsorption develop.

Celiac Disease Foundation, 20350 Ventura Blvd, Suite #240, Woodland Hills, CA 91364. https://celiac.org

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2. Whipple Disease

ESSENTIALS OF DIAGNOSIS

- Multisystem disease.
- Fever, lymphadenopathy, arthralgias.
- Weight loss, malabsorption, chronic diarrhea.
- Duodenal biopsy with periodic acid-Schiff (PAS)-positive macrophages with characteristic bacillus.

General Considerations

Whipple disease is a rare multisystem illness with an estimated prevalence of 1 per 100,000 caused by infection with the bacillus *Tropheryma whipplei*. It may occur at any age but most commonly affects White men in the fourth to sixth decades. The source of infection is unknown, but no cases of human-to-human spread have been documented.

Clinical Findings

A. Symptoms and Signs

The clinical manifestations are protean; however, the most common are arthralgias, diarrhea, abdominal pain, and weight loss. Arthralgias or a migratory, nondeforming arthritis occurs in 80% and is typically the first symptom experienced. GI symptoms occur in approximately 75% of cases. They include abdominal pain, diarrhea, and some degree of malabsorption with distention, flatulence, and steatorrhea. Weight loss is the most common presenting symptom—seen in almost all patients. Loss of protein due to intestinal or lymphatic involvement may result in protein-losing enteropathy with hypoalbuminemia and edema. In the absence of GI symptoms, the diagnosis often is delayed for several years. Intermittent low-grade fever occurs in over 50% of cases.

Physical examination may reveal hypotension (a late finding), low-grade fever, and evidence of malabsorption (see Table 15–11). Lymphadenopathy is present in 50%. Heart murmurs due to valvular involvement may be evident. Peripheral joints may be enlarged or warm, and peripheral edema may be present. Neurologic findings are protean, and include ophthalmoplegia, dementia (confusion, memory loss), cerebellar ataxia, chronic meningitis, myelopathy, and seizures. Hyperpigmentation on sun-exposed areas is evident in up to 40%.

B. Laboratory Findings

If significant malabsorption is present, patients may have laboratory abnormalities as outlined in Table 15–11. There may be steatorrhea.

C. Histologic Evaluation

The diagnosis of Whipple disease is established in 90% of cases by endoscopic biopsy of the duodenum with histologic evaluation, which demonstrates infiltration of the lamina propria with PAS-positive macrophages that contain gram-positive bacilli (which are not acid-fast) and dilation of the lacteals. The remainder of cases are diagnosed by *T whipplei*–specific PCR or immunohistochemistry of duodenal biopsies or extraintestinal fluids (cerebrospinal, synovial) or tissue (lymph nodes, synovium, endocardium). The sensitivity of PCR is 97% and the specificity 100%. Because asymptomatic CNS infection occurs in 40% of patients, examination of the cerebrospinal fluid by PCR for *T whipplei* should be performed routinely.

Differential Diagnosis

Whipple disease should be considered in patients who present with signs of malabsorption, fever of unknown origin, lymphadenopathy, seronegative arthritis, culture-negative endocarditis, or multisystem disease. Small bowel biopsy readily distinguishes Whipple disease from other mucosal malabsorptive disorders, such as celiac disease.

Treatment

Antibiotic therapy results in a dramatic clinical improvement within several weeks, even in some patients with neurologic involvement. The optimal regimen is unknown.

Complete clinical response usually is evident within 1–3 months; however, relapse may occur in up to one-third of patients after discontinuation of treatment. Therefore, prolonged treatment for at least 1 year is required. Drugs that cross the blood-brain barrier are preferred. A randomized controlled trial in 40 patients with 3–10 years' follow-up demonstrated 100% remission with either ceftriaxone 1 g intravenously twice daily or meropenem 1 g intravenously three times daily for 2 weeks, followed by trimethoprim-sulfamethoxazole 160/800 mg twice daily for 12 months. After treatment, repeat duodenal biopsies for histologic analysis and cerebrospinal fluid PCR should be obtained every 6 months for at least 1 year. The absence of PAS-positive material predicts a low likelihood of clinical relapse.

Prognosis

If untreated, the disease is fatal. Because some neurologic signs may be permanent, the goal of treatment is to prevent this progression. Patients must be followed closely after treatment for signs of symptom recurrence.

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3. Bacterial Overgrowth

ESSENTIALS OF DIAGNOSIS

- Symptoms of diarrhea, bloating, and flatulence.
- Advanced cases associated with weight loss, steatorrhea, and deficiencies of iron or vitamins A, D, and B_{12}.
- Diagnosis suggested by breath tests using glucose or lactulose as substrates.
- Diagnosis confirmed by jejunal aspiration with quantitative bacterial cultures.

General Considerations

The small intestine normally contains a small number of bacteria. Bacterial overgrowth in the small intestine of whatever cause may result in malabsorption via several mechanisms. Passage of malabsorbed bile acids and carbohydrates into the colon leads to an osmotic and secretory diarrhea and increased flatulence.

Causes of bacterial overgrowth include (1) gastric achlorhydria (including PPI therapy); (2) anatomic abnormalities of the small intestine with stagnation (afferent limb of Billroth II gastrojejunostomy, resection of ileocecal valve, small intestine diverticula, obstruction, blind loop); (3) small intestine motility disorders (vagotomy, systemic sclerosis, diabetic enteropathy, chronic intestinal pseudo-obstruction); (4) gastrocolic or coloenteric fistula (Crohn disease, malignancy, surgical resection); and (5) miscellaneous disorders. Bacterial overgrowth is an important cause of diarrhea in older patients, perhaps because of decreased gastric acidity or impaired intestinal motility. It may also be present in a subset of patients with IBS.

Clinical Findings

Many patients with bacterial overgrowth are asymptomatic. Symptoms are nonspecific and include diarrhea, bloating, flatulence, and sometimes steatorrhea with weight loss. Bacterial overgrowth should be considered in any patient with these symptoms, especially patients with a predisposing cause (such as prior GI surgery) and older adults with unexplained diarrhea and weight loss. Bacterial synthesis of folic acid and consumption of cobalamin may cause elevated serum folate and decreased vitamin B_{12} levels. Severe cases may result in clinically significant vitamin and mineral deficiencies, including fat-soluble vitamins A or D, and low serum albumin (Table 15–11). A specific diagnosis can be established firmly only by an aspirate and culture of distal duodenal secretion that demonstrates over 10^3 organisms/mL. However, this is an invasive and laborious test that requires careful collection and culturing techniques and therefore is not available in most clinical settings. Noninvasive breath hydrogen and methane tests with glucose or lactulose as substrates are generally preferred because of their ease of use. Following ingestion of glucose 75 g or lactulose 10 g, a rise in exhaled breath hydrogen of 20 ppm or methane of 10 ppm or more within 90 minutes is suggestive of bacterial overgrowth and has 65% diagnostic agreement with small bowel cultures. A small bowel study (CT or MR enterography, barium radiography) may be obtained to look for mechanical factors predisposing to intestinal stasis.

A 2020 American College of Gastroenterology guideline suggests breath testing when bacterial overgrowth is suspected. However, many clinicians prefer to use an empiric antibiotic trial as a diagnostic and therapeutic strategy.

Treatment

Where possible, the anatomic defect that has potentiated bacterial overgrowth should be corrected. Otherwise, treatment for 7–10 days with oral broad-spectrum antibiotics improves symptoms in up to 90% of patients for weeks to months. Recommended regimens include ciprofloxacin, 250 mg twice daily; amoxicillin clavulanate, 875 mg twice daily; trimethoprim-sulfamethoxazole (one double-strength tablet) twice daily; rifaximin, 400–550 mg three times daily; or a combination of neomycin, 500 mg twice daily, plus metronidazole, 250 mg three times daily.

Within 6 months of completing antibiotic therapy, symptoms recur in over 25% of patients. In patients with more frequent symptomatic relapse, cyclic antibiotic therapy (eg, 1 week out of 4) may be sufficient. Continuous antibiotics should be avoided, if possible, to avoid development of bacterial antibiotic resistance.

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Quigley EM et al. AGA Clinical Practice Update on small intestinal bacterial overgrowth: expert review. Gastroenterology. 2020;159:1526. [PMID: 32679220]

4. Short Bowel Syndrome

Short bowel syndrome is the malabsorptive condition that arises secondary to removal of significant segments of the small intestine. The most common causes in adults are Crohn disease, mesenteric infarction, radiation enteritis, volvulus, tumor resection, and trauma. The type and degree of malabsorption depend on the length and site of the resection and the degree of adaptation of the remaining bowel.

Terminal Ileal Resection

Resection of the terminal ileum results in malabsorption of bile salts and vitamin B_{12}, which are normally absorbed in this region. Patients with low serum vitamin B_{12} levels or resection of over 50 cm of ileum require monthly subcutaneous or intramuscular vitamin B_{12} injections. In patients with less than 100 cm of ileal resection, bile salt malabsorption stimulates fluid secretion from the colon, resulting in watery diarrhea. This may be treated with administration of bile salt-binding resins one to three times daily with meals (cholestyramine, 2–4 g/day orally, colestipol tablets, 2 g orally, or colesevelam, 625 mg orally). Resection of over 100 cm of ileum leads to a reduction in the bile salt pool that results in steatorrhea and malabsorption of fat-soluble vitamins. Treatment is with a low-fat diet and vitamins supplemented with medium-chain triglycerides, which do not require micellar solubilization. Unabsorbed fatty acids bind with calcium, reducing its absorption and enhancing the absorption of oxalate. Oxalate kidney stones may develop. Calcium supplements should be administered to bind oxalate and increase serum calcium. Cholesterol gallstones due to decreased bile salts are common also. In patients with resection of the ileocolonic valve, bacterial overgrowth may occur in the small intestine, further complicating malabsorption.

Extensive Small Bowel Resection

Resection of up to 40–50% of the total length of small intestine usually is well tolerated. A more massive resection may result in "short bowel syndrome," characterized by weight loss and diarrhea due to nutrient, water, and electrolyte malabsorption. If the colon is preserved, 100 cm of proximal jejunum may be sufficient to maintain adequate oral nutrition with a low-fat, high–complex carbohydrate diet, though fluid and electrolyte losses may still be significant. In patients in whom the colon has been removed, at least 200 cm of proximal jejunum is typically required to maintain oral nutrition. Antidiarrheal agents (loperamide, 2–4 mg orally three times daily) slow transit and reduce diarrheal volume. Octreotide reduces intestinal transit time and fluid and electrolyte secretion. Gastric hypersecretion initially complicates intestinal resection and should be treated with PPIs.

Patients with less than 100–200 cm of proximal jejunum remaining almost always require parenteral nutrition. Teduglutide (recombinant) is a glucagon-like peptide-2 analogue that stimulates small bowel growth and absorption and is FDA approved for the treatment of short bowel syndrome. In clinical trials, it resulted in a reduced need for parenteral nutrition. Small intestine transplantation has a reported 5-year graft survival rate of 40%. Currently, it is performed chiefly in patients in whom serious problems develop due to parenteral nutrition.

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Harpain F et al. Teduglutide in short bowel syndrome patients: a way back to normal life? JPEN J Parenter Enteral Nutr. 2022;46:300. [PMID: 34614239]
Massironi S et al. Understanding short bowel syndrome: current status and future perspectives. Dig Liver Dis. 2020;52:253. [PMID: 31892505]
Pironi L. Translation of evidence into practice with teduglutide in the management of adults with intestinal failure due to short-bowel syndrome: a review of recent literature. JPEN J Parenter Enteral Nutr. 2020;44:968. [PMID: 31802516]
Sadowski DC et al. Canadian Association of Gastroenterology clinical practice guideline on the management of bile acid diarrhea. Clin Gastroenterol Hepatol. 2020;18:24. [PMID: 31526844]

5. Lactase Deficiency

ESSENTIALS OF DIAGNOSIS

- Diarrhea, bloating, flatulence, and abdominal pain after ingestion of milk-containing products.
- Diagnosis supported by symptomatic improvement on lactose-free diet.
- Diagnosis confirmed by hydrogen breath test.

General Considerations

Lactase is a brush border enzyme that hydrolyzes the disaccharide lactose into glucose and galactose. The concentration of lactase enzyme levels is high at birth but declines steadily in most people of non-European ancestry during childhood and adolescence and into adulthood. As many as 90% of Asian Americans, 70% of African Americans, 95% of Native Americans, 50% of Mexican Americans, and 60% of Jewish Americans are lactose intolerant compared with less than 25% of White adults. Lactase deficiency may also arise secondary to other GI disorders that affect the proximal small intestinal mucosa. These include Crohn disease, celiac disease, viral gastroenteritis, giardiasis, short bowel syndrome, and malnutrition. Malabsorbed lactose is fermented by intestinal bacteria, producing gas and organic acids. The nonmetabolized lactose and organic acids result in an increased stool osmotic load with an obligatory fluid loss.

Clinical Findings

A. Symptoms and Signs

Patients have great variability in clinical symptoms, depending both on the severity of lactase deficiency and the amount of lactose ingested. Because of the nonspecific nature of these symptoms, there is a tendency for both lactose-intolerant and lactose-tolerant individuals to mistakenly attribute a variety of abdominal symptoms to lactose intolerance. Most patients with lactose intolerance can drink at least one 8-oz serving of milk daily (12 g of lactose) without symptoms, though rare patients have almost complete intolerance. With mild to moderate amounts of lactose malabsorption, patients may experience bloating, abdominal cramps, and flatulence. With higher lactose ingestions, an osmotic diarrhea will result. Isolated lactase deficiency does not result in other signs of malabsorption or weight loss. If these findings are present, other GI disorders should be pursued.

B. Laboratory Findings

The most widely available test for the diagnosis of lactase deficiency is the hydrogen breath test. After ingestion of 50 g of lactose, a rise in breath hydrogen of more than 20 ppm within 90 minutes is a positive test, indicative of bacterial carbohydrate metabolism. In clinical practice, many clinicians prescribe an empiric trial of a lactose-free diet for 2 weeks. Resolution of symptoms (bloating, flatulence, diarrhea) is suggestive of lactase deficiency (though a placebo response cannot be excluded) and may be confirmed, if necessary, with a hydrogen breath test.

Differential Diagnosis

The symptoms of late-onset lactose intolerance are nonspecific and may mimic several GI disorders, such as inflammatory bowel disease, mucosal malabsorptive disorders, IBS, and pancreatic insufficiency. Furthermore, lactase deficiency frequently develops secondary to other GI disorders (as listed above).

Treatment

The goal of treatment in patients with isolated lactase deficiency is achieving patient comfort. Patients usually find their "threshold" of intake at which symptoms will occur. Foods that are high in lactose include milk (12 g/cup), ice cream (9 g/cup), and cottage cheese (8 g/cup). Aged cheeses have a lower lactose content (0.5 g/oz). Unpasteurized yogurt contains bacteria that produce lactase and is generally well tolerated.

By spreading dairy product intake throughout the day in quantities of less than 12 g of lactose (one cup of milk), most patients can take dairy products without symptoms and do not require lactase supplements. Most food markets provide milk that has been pretreated with lactase, rendering it 100% lactose free (Fairlife). Lactase enzyme replacement is commercially available as nonprescription formulations (Lactaid, Lactrase, Dairy Ease). Caplets or drops of lactase may be taken with milk products, improving lactose absorption and eliminating symptoms. The number of caplets ingested depends on the degree of lactose intolerance. Patients who choose to restrict or eliminate milk products should consider calcium supplementation (calcium citrate 650 mg 2 tablets orally two times daily) to meet calcium intake needs and reduce risk of osteoporosis.

Catanzaro R et al. Lactose intolerance: an update on its pathogenesis, diagnosis, and treatment. Nutr Res. 2021;89:23. [PMID: 33887513]

INTESTINAL MOTILITY DISORDERS

1. Acute Paralytic Ileus

ESSENTIALS OF DIAGNOSIS

- Precipitating factors: surgery, peritonitis, electrolyte abnormalities, medications, severe medical illness.
- Nausea, vomiting, obstipation, distention.
- Minimal abdominal tenderness; decreased bowel sounds.
- Plain abdominal radiography with gas and fluid distention in small and large bowel.

General Considerations

Ileus is a condition in which there is neurogenic failure or loss of peristalsis in the intestine in the absence of any mechanical obstruction. It is commonly seen in hospitalized patients as a result of (1) intra-abdominal processes such as recent GI or abdominal surgery or peritoneal irritation (peritonitis, pancreatitis, ruptured viscus, hemorrhage); (2) severe medical illness such as pneumonia, respiratory failure requiring intubation, sepsis or severe infections, uremia, diabetic ketoacidosis, and electrolyte abnormalities (hypokalemia, hypercalcemia, hypomagnesemia, hypophosphatemia); and (3) medications that affect intestinal motility (opioids, anticholinergics, phenothiazines). Following surgery, small intestinal motility usually normalizes first (often within hours), followed by the stomach (24–48 hours), and the colon (48–72 hours). Postoperative ileus is reduced with minimally invasive (eg, laparoscopic) surgery, by the use of patient-controlled or epidural analgesia, and by avoidance of intravenous opioids as well as early ambulation, gum chewing, and initiation of a clear liquid diet.

Clinical Findings

A. Symptoms and Signs

Patients who are conscious report mild diffuse, continuous abdominal discomfort with nausea and vomiting. Generalized abdominal distention is present with minimal abdominal tenderness but no signs of peritoneal irritation

(unless due to the primary disease). Bowel sounds are diminished to absent.

B. Laboratory Findings

The laboratory abnormalities are attributable to the underlying condition. Serum electrolytes (sodium, potassium), magnesium, phosphorus, and calcium, should be obtained to exclude abnormalities as contributing factors.

C. Imaging

Plain film radiography of the abdomen demonstrates distended gas-filled loops of the small and large intestine. Air-fluid levels may be seen. Under some circumstances, it may be difficult to distinguish ileus from partial small bowel obstruction. A CT scan may be useful in such instances to exclude mechanical obstruction, especially in postoperative patients.

Differential Diagnosis

Ileus must be distinguished from mechanical obstruction of the small bowel or proximal colon. Pain from small bowel mechanical obstruction is usually intermittent, cramping, and associated initially with profuse vomiting. Acute gastroenteritis, acute appendicitis, and acute pancreatitis may all present with ileus.

Treatment

The primary medical or surgical illness that has precipitated adynamic ileus should be treated. Most cases of ileus respond to restriction of oral intake with gradual liberalization of diet as bowel function returns. Severe or prolonged ileus requires nasogastric suction and parenteral administration of fluids and electrolytes. Alvimopan is a peripherally acting mu-opioid receptor antagonist with limited absorption or systemic activity that reverses opioid-induced inhibition of intestinal motility.

Wells CI et al. Post-operative ileus: definitions, mechanisms and controversies. ANZ J Surg. 2022;92:62. [PMID: 34676664]

2. Acute Colonic Pseudo-Obstruction (Ogilvie Syndrome)

ESSENTIALS OF DIAGNOSIS

- Severe abdominal distention.
- Arises in postoperative state or with severe medical illness.
- May be precipitated by electrolyte imbalances, medications.
- Absent to mild abdominal pain; minimal tenderness.
- Massive dilation of cecum or right colon.

General Considerations

Spontaneous massive dilation of the cecum and proximal colon may occur in many different settings in hospitalized patients. Progressive cecal dilation may lead to ischemia and spontaneous perforation with dire consequences. The risk of perforation increases with duration of distention beyond 6 days but correlates poorly with absolute cecal size. Early detection and management are important to reduce morbidity and mortality. Colonic pseudo-obstruction is most commonly detected in postsurgical patients (mean 3–5 days), after trauma, and in medical patients with respiratory failure, metabolic imbalance, malignancy, MI, heart failure, pancreatitis, or a recent neurologic event (stroke, subarachnoid hemorrhage, trauma). Liberal use of opioids or anticholinergic agents may precipitate colonic pseudo-obstruction in susceptible patients.

Clinical Findings

A. Symptoms and Signs

Many patients are on ventilatory support or are unable to report symptoms due to altered mental status. Abdominal distention is frequently noted by the clinician as the first sign, often leading to a plain film radiograph that demonstrates colonic dilation. Some patients are asymptomatic, although most report constant but mild abdominal pain. Nausea and vomiting may be present. Bowel movements may be absent, but up to 40% of patients continue to pass flatus or stool. Abdominal tenderness with some degree of guarding or rebound tenderness may be detected; however, signs of peritonitis are absent unless perforation has occurred. Bowel sounds may be normal or decreased.

B. Laboratory Findings

Laboratory findings reflect the underlying medical or surgical problems. Serum sodium, potassium, magnesium, phosphorus, and calcium should be obtained to exclude abnormalities as contributing factors. Significant fever or leukocytosis raises concern for colonic ischemia or perforation.

C. Imaging

Radiographs demonstrate colonic dilation, usually confined to the cecum and proximal colon. The upper limit of normal for cecal size is 9 cm. A cecal diameter greater than 10–12 cm is associated with an increased risk of colonic perforation. Varying amounts of small intestinal dilation and air-fluid levels due to adynamic ileus may be seen. Generally, a CT scan should be obtained to exclude a distal colonic mechanical obstruction due to malignancy, volvulus, or fecal impaction.

Differential Diagnosis

Colonic pseudo-obstruction should be distinguished from distal colonic mechanical obstruction (as above) and toxic megacolon, which is acute dilation of the colon due to inflammation (inflammatory bowel disease) or infection (*C difficile*–associated colitis, CMV). Patients with toxic

megacolon manifest fever; dehydration; significant abdominal pain; leukocytosis; and diarrhea, which is often bloody.

Treatment

Conservative treatment is the appropriate first step for patients with no or minimal abdominal tenderness, no fever, no leukocytosis, and a cecal diameter smaller than 12 cm. The underlying illness is treated appropriately. A nasogastric tube and a rectal tube should be placed. Patients should be ambulated or periodically rolled from side to side and to the knee-chest position in an effort to promote expulsion of colonic gas. All drugs that reduce intestinal motility, such as opioids, anticholinergics, and calcium channel blockers, should be discontinued if possible. Enemas may be administered judiciously if large amounts of stool are evident on radiography. Oral laxatives are not helpful and may cause perforation, pain, or electrolyte abnormalities.

Conservative treatment is successful in over 80% of cases within 1–2 days. Patients must be watched for signs of worsening distention or abdominal tenderness. Cecal size should be assessed by abdominal radiographs every 12 hours. Intervention should be considered in patients with any of the following: (1) no improvement or clinical deterioration after 24–48 hours of conservative therapy; (2) cecal dilation greater than 10 cm for a prolonged period (more than 3–4 days); or (3) patients with cecal dilation greater than 12 cm. Neostigmine injection should be given unless contraindicated. A single dose (2 mg intravenously) results in rapid (within 30 minutes) colonic decompression in 75–90% of patients. Cardiac monitoring during neostigmine infusion is indicated for possible bradycardia that may require atropine administration. Colonoscopic decompression is indicated in patients who fail to respond to neostigmine. Colonic decompression with aspiration of air or placement of a decompression tube is successful in 70% of patients. However, the procedure is technically difficult in an unprepared bowel and has been associated with perforations in the distended colon. Dilation recurs in up to 50% of patients. In patients in whom colonoscopy is unsuccessful, a tube cecostomy can be created through a small laparotomy or with percutaneous radiologically guided placement.

Prognosis

In most cases, the prognosis is related to the underlying illness. The risk of perforation or ischemia is increased with cecal diameter more than 12 cm and when distention has been present for more than 6 days. With aggressive therapy, the development of perforation is unusual.

Jeong SJ et al. Endoscopic management of benign colonic obstruction and pseudo-obstruction. Clin Endosc. 2020;53:18. [PMID: 31645090]

Naveed M et al. American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in the management of acute colonic pseudo-obstruction and colonic volvulus. Gastrointest Endosc. 2020;91:228. [PMID: 31791596]

3. Chronic Intestinal Pseudo-Obstruction & Gastroparesis

Gastroparesis and chronic intestinal pseudo-obstruction are chronic conditions characterized by intermittent, waxing and waning symptoms and signs of gastric or intestinal obstruction in the absence of any mechanical lesions to account for the findings. They are caused by a heterogeneous group of endocrine disorders (diabetes mellitus, hypothyroidism, cortisol deficiency), postsurgical conditions (vagotomy, partial gastric resection, fundoplication, gastric bypass, Whipple procedure), neurologic conditions (Parkinson disease, muscular and myotonic dystrophy, autonomic dysfunction, multiple sclerosis, postpolio syndrome, porphyria), rheumatologic syndromes (progressive systemic sclerosis), infections (postviral, Chagas disease), amyloidosis, paraneoplastic syndromes, medications, and eating disorders (anorexia); a cause may not always be identified.

Clinical Findings

A. Symptoms and Signs

Gastric involvement leads to chronic or intermittent symptoms of gastroparesis with early satiety, nausea, vomiting (1–3 hours after meals) and epigastric pain. Upper abdominal symptoms correlate poorly with the severity of gastric emptying. Patients with predominantly small bowel involvement may have abdominal distention, vomiting, diarrhea, and varying degrees of malnutrition. Abdominal pain is not common and should prompt investigation for structural causes of obstruction. Bacterial overgrowth in the stagnant intestine may result in malabsorption. Colonic involvement may result in constipation or alternating diarrhea and constipation.

B. Imaging

Plain film radiography may demonstrate dilation of the esophagus, stomach, small intestine, or colon resembling ileus or mechanical obstruction. Mechanical obstruction of the stomach, small intestine, or colon is much more common than gastroparesis or intestinal pseudo-obstruction and must be excluded with endoscopy or CT enterography, especially in patients with prior surgery, recent onset of symptoms, or abdominal pain. In cases of unclear origin, studies based on the clinical picture are obtained to exclude underlying systemic disease. Gastric scintigraphy with a low-fat solid meal remains the preferred method for assessing gastric emptying. Gastric retention of 60% after 2 hours or more than 10% after 4 hours is abnormal. A wireless motility capsule and a nonradioactive or 13-C labeled breath test using blue-green algae (*Spirulina platensis*) also are available. Small bowel manometry is useful for distinguishing visceral from myopathic disorders and for excluding cases of mechanical obstruction that are otherwise difficult to diagnose by endoscopy or radiographic studies.

Treatment

There is no specific therapy for gastroparesis or pseudo-obstruction. Acute exacerbations are treated with

nasogastric suction and intravenous fluids. Long-term treatment is directed at maintaining nutrition. Patients should eat small, frequent meals that are low in fiber, milk, gas-forming foods, and fat. Foods that are well tolerated include tea, ginger ale, soup, white rice, potatoes and sweet potatoes, fish, gluten-free foods, and applesauce. Some patients may require liquid enteral supplements. Agents that reduce GI motility (opioids, anticholinergics) should be avoided. In diabetic patients, glucose levels should be maintained below 200 mg/dL since hyperglycemia may slow gastric emptying even in the absence of diabetic neuropathy, and amylin and GLP-1 analogs (exenatide or pramlintide) should be discontinued.

Currently available prokinetic agents have shown limited improvement of gastric emptying or upper GI symptoms in patients with gastroparesis. Metoclopramide (5–20 mg orally or 5–10 mg intravenously or subcutaneously four times daily) may enhance gastric emptying but not small bowel dysmotility. Since the use of metoclopramide for more than 3 months is associated with a less than 1% risk of tardive dyskinesia, patients are advised to discontinue the medication if neuromuscular side effects, particularly involuntary movements, develop. Older patients are at greatest risk. In 2019, a small, blinded, crossover trial involving 34 patients with confirmed gastroparesis showed that prucalopride, a serotonin 5-HT_4-receptor agonist (currently FDA approved for treatment of chronic constipation), significantly improved gastric emptying and symptoms after 2 weeks of therapy (2 mg daily orally) compared with placebo. Several uncontrolled studies report symptom improvement with endoscopic modalities that reduce intrapyloric pressure, including botulinum toxin injection, dilation, and myotomy (G-POEM). In a systematic review of 10 studies involving 292 patients, endoscopic pyloromyotomy led to symptomatic improvement in 84%. Bacterial overgrowth should be treated with intermittent antibiotics. Patients with predominant small bowel distention may require a venting gastrostomy to relieve distress. Some patients may require placement of a jejunostomy for long-term enteral nutrition. Patients unable to maintain adequate enteral nutrition require TPN or small bowel transplantation. Difficult cases should be referred to centers with expertise in this area.

Abdelfatah MM et al. Long-term outcome of gastric per-oral endoscopic pyloromyotomy in treatment of gastroparesis. Clin Gastroenterol Hepatol. 2021;19:816. [PMID: 32450364]
Carlin JL et al. Efficacy and safety of tradipitant in patients with diabetic and idiopathic gastroparesis in a randomized, placebo-controlled trial. Gastroenterology. 2021;160:76. [PMID: 32693185]
Lacy BE et al. Controversies in gastroparesis: discussing the sticky points. Am J Gastroenterol. 2021;116:1572. [PMID: 33767098]
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Vijayvargiya P et al. Effects of promotility agents on gastric emptying and symptoms: a systematic review and meta-analysis. Gastroenterology. 2019;156:1650. [PMID: 30711628]

APPENDICITIS

ESSENTIALS OF DIAGNOSIS

- *Early:* periumbilical pain; *later:* right lower quadrant pain and tenderness.
- Anorexia, nausea and vomiting, obstipation.
- Tenderness or localized rigidity at McBurney point.
- Low-grade fever and leukocytosis.

General Considerations

Appendicitis is the most common abdominal surgical emergency, affecting approximately 10% of the population. It occurs most commonly between the ages of 10 and 30 years. It is initiated by obstruction of the appendix by a fecalith, inflammation, foreign body, or neoplasm. Obstruction leads to increased intraluminal pressure, venous congestion, infection, and thrombosis of intramural vessels. If untreated, gangrene and perforation develop within 36 hours.

Clinical Findings

A. Symptoms and Signs

Appendicitis usually begins with vague, often colicky periumbilical or epigastric pain. Within 12 hours the pain shifts to the right lower quadrant, manifested as a steady ache that is worsened by walking or coughing. Almost all patients have nausea with one or two episodes of vomiting. Protracted vomiting or vomiting that begins before the onset of pain suggests another diagnosis. A sense of constipation is typical, and some patients administer cathartics in an effort to relieve their symptoms—though some report diarrhea. Low-grade fever (below 38°C) is typical; high fever or rigors suggest another diagnosis or appendiceal perforation.

On physical examination, localized tenderness with guarding in the right lower quadrant can be elicited with gentle palpation with one finger. When asked to cough, patients may be able to precisely localize the painful area, a sign of peritoneal irritation. Light percussion may also elicit pain. Although rebound tenderness is also present, it is unnecessary to elicit this finding if the above signs are present. The psoas sign (pain on passive extension of the right hip) and the obturator sign (pain with passive flexion and internal rotation of the right hip) are indicative of adjacent inflammation and strongly suggestive of appendicitis.

B. Atypical Presentations of Appendicitis

Owing to the variable location of the appendix, there are a number of "atypical" presentations. Because the retrocecal appendix does not touch the anterior abdominal wall, the pain remains less intense and poorly localized; abdominal tenderness is minimal and may be elicited in the right flank.

The psoas sign may be positive. With pelvic appendicitis, there is pain in the lower abdomen, often on the left, with an urge to urinate or defecate. Abdominal tenderness is absent, but tenderness is evident on pelvic or rectal examination; the obturator sign may be present. In older adult patients, the diagnosis of appendicitis is often delayed because patients present with minimal, vague symptoms and mild abdominal tenderness.

C. Laboratory Findings

Moderate leukocytosis (10,000–20,000/mcL [10–20 × 10^9/L]) with neutrophilia is common. Microscopic hematuria and pyuria are present in 25% of patients.

D. Imaging

Both abdominal ultrasound and CT are useful in diagnosing appendicitis as well as excluding other diseases presenting with similar symptoms, including adnexal disease in younger women. However, CT appears to be more accurate (sensitivity 94%, specificity 95%, positive likelihood ratio 13.3, negative likelihood ratio 0.09). Abdominal CT is also useful in cases of suspected appendiceal perforation to diagnose a periappendiceal abscess. In patients in whom there is a clinically high suspicion of appendicitis, some surgeons feel that preoperative diagnostic imaging is unnecessary. However, studies suggest that even in this group, imaging studies suggest an alternative diagnosis in up to 15%.

Differential Diagnosis

Given its frequency and myriad presentations, appendicitis should be considered in the differential diagnosis of all patients with abdominal pain. A several-hour period of close observation with reassessment usually clarifies the diagnosis. In a 2020 retrospective review of 123,711 adults with appendicitis, the diagnosis was more commonly missed in women, patients with comorbidities, and patients who experienced abdominal pain with constipation. Absence of classic migration of pain (from epigastrium to right lower abdomen); right lower quadrant pain; fever; or guarding each makes appendicitis less likely. Widespread use of ultrasonography and CT has reduced the number of incorrect diagnoses to less than 2%. Still, in some cases, diagnostic laparotomy or laparoscopy is required.

The most common causes of diagnostic confusion are gastroenteritis and gynecologic disorders. Viral gastroenteritis presents with nausea, vomiting, low-grade fever, and diarrhea and can be difficult to distinguish from appendicitis. The onset of vomiting before pain makes appendicitis less likely. As a rule, the pain of gastroenteritis is more generalized and the tenderness less well localized. Acute salpingitis or tubo-ovarian abscess should be considered in young, sexually active women with fever and bilateral abdominal or pelvic tenderness. A twisted ovarian cyst may also cause sudden severe pain. The sudden onset of lower abdominal pain in the middle of the menstrual cycle suggests mittelschmerz. Sudden severe abdominal pain with diffuse pelvic tenderness and shock suggests a ruptured ectopic pregnancy. A positive pregnancy test and pelvic ultrasonography are diagnostic. Retrocecal or retroileal appendicitis (often associated with pyuria or hematuria) may be confused with ureteral colic or pyelonephritis. Other conditions that may resemble appendicitis are diverticulitis, carcinoid of the appendix, perforated colonic cancer, Crohn ileitis, perforated peptic ulcer, cholecystitis, and mesenteric adenitis. It is virtually impossible to distinguish appendicitis from Meckel diverticulitis, but both require surgical treatment.

Complications

Perforation occurs in 20% of patients and should be suspected in patients with pain persisting for over 36 hours, high fever, diffuse abdominal tenderness or peritoneal findings, a palpable abdominal mass, or marked leukocytosis. Localized perforation results in a contained abscess, usually in the pelvis. A free perforation leads to suppurative peritonitis with toxicity. Septic thrombophlebitis (pylephlebitis) of the portal venous system is rare and suggested by high fever, chills, bacteremia, and jaundice.

Treatment

The treatment of early, uncomplicated appendicitis is surgical appendectomy in most patients. When possible, a laparoscopic approach is preferred to open laparotomy. Prior to surgery, patients should be given broad-spectrum antibiotics with gram-negative and anaerobic coverage to reduce the incidence of postoperative infections. Recommended preoperative intravenous regimens include cefoxitin or cefotetan 1–2 g every 8 hours; ampicillin-sulbactam 3 g every 6 hours; or ertapenem 1 g as a single dose. Up to 80–90% of patients with uncomplicated appendicitis treated with antibiotics alone for 7 days have resolution of symptoms and signs. Therefore, conservative management with antibiotics alone may be considered in patients with a nonperforated appendicitis with surgical contraindications or with a strong preference to avoid surgery; however, appendectomy generally still is recommended in most patients to prevent recurrent appendicitis (20–35% within 1 year).

Emergency appendectomy is required in patients with perforated appendicitis with generalized peritonitis. The optimal treatment of stable patients with perforated appendicitis and a contained abscess is controversial. Surgery in this setting can be difficult. Many recommend percutaneous CT-guided drainage of the abscess with intravenous fluids and antibiotics to allow the inflammation to subside. An interval appendectomy may be performed after 6 weeks to prevent recurrent appendicitis.

Prognosis

The mortality rate from uncomplicated appendicitis is extremely low. Even with perforated appendicitis, the mortality rate in most groups is only 0.2%, though it approaches 15% in older adults.

Di Saverio S et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World J Emerg Surg. 2020;15:27. [PMID: 32295644]

Flum DR et al. A randomized trial comparing antibiotics with appendectomy for appendicitis. N Engl J Med. 2020;383:1907. [PMID: 33017106]
Mahajan P et al. Factors associated with potentially missed diagnosis of appendicitis in the emergency department. JAMA Netw Open. 2020;3:e200612. [PMID: 32150270]
Sippola S et al. Effect of oral moxifloxacin versus intravenous ertapenem plus oral levofloxacin for treatment of uncomplicated acute appendicitis: the APPAC II randomized clinical trial. JAMA. 2021;325:353. [PMID: 33427870]

INTESTINAL TUBERCULOSIS

Intestinal tuberculosis is common in underdeveloped countries but rare in the United States except in immigrant groups or in patients with untreated AIDS. It is caused by both *Mycobacterium tuberculosis* and *M bovis.* Active pulmonary disease is present in less than 50% of patients. The most frequent site of involvement is the ileocecal region; however, any region of the GI tract may be involved. Patients may be without symptoms or complain of chronic abdominal pain, obstructive symptoms, weight loss, and diarrhea. An abdominal mass may be palpable. Complications include intestinal obstruction, hemorrhage, and fistula formation. The purified protein derivative (PPD) skin test may be negative, especially in patients with weight loss or AIDS. Abdominal CT may show thickening of the cecum and ileocecal valve and massive lymphadenopathy. Colonoscopy may demonstrate an ulcerated mass, multiple ulcers with steep edges and adjacent small sessile polyps, small ulcers or erosions, or small diverticula, most commonly in the ileocecal region. The differential diagnosis includes Crohn disease, carcinoma, lymphoma, and intestinal amebiasis. The diagnosis is established by either endoscopic or surgical biopsy revealing acid-fast bacilli, caseating granuloma, or positive cultures for the organism. Detection of tubercle bacilli in biopsy specimens by PCR is now the most sensitive means of diagnosis.

Treatment with standard antituberculous regimens (Tables 9–14 and 9–15) is effective.

Lu S et al. Clinical diagnosis and endoscopic analysis of 10 cases of intestinal tuberculosis. Medicine (Baltimore). 2020;99:e21175. [PMID: 32664157]

PROTEIN-LOSING ENTEROPATHY

Protein-losing enteropathy comprises a number of conditions that result in excessive loss of serum proteins into the GI tract.

Hypoalbuminemia is the sine qua non of protein-losing enteropathy. However, other serum proteins such as alpha-1-antitrypsin also are lost from the gut epithelium. In protein-losing enteropathy caused by lymphatic obstruction, loss of lymphatic fluid commonly results in lymphocytopenia (less than 1000/mcL), hypoglobulinemia, and hypocholesterolemia.

In most cases, protein-losing enteropathy is recognized as a sequela of a known GI disorder. In patients in whom the cause is unclear, evaluation is indicated and is guided by the clinical suspicion. Protein-losing enteropathy must be distinguished from other causes of hypoalbuminemia, which include liver disease and nephrotic syndrome, and from heart failure. Protein-losing enteropathy is confirmed by determining the gut alpha-1-antitrypsin clearance (24-hour volume of feces × stool concentration of alpha-1-antitrypsin ÷ serum alpha-1-antitrypsin concentration). A clearance of more than 27 mL/24 hours is abnormal.

Laboratory evaluation of protein-losing enteropathy includes serum protein electrophoresis, lymphocyte count, and serum cholesterol to look for evidence of lymphatic obstruction. Serum ANA and C3 levels are useful to screen for autoimmune disorders. Stool samples should be examined for ova and parasites. Evidence of malabsorption is evaluated by means of a stool qualitative fecal fat determination. Intestinal imaging is performed with small bowel enteroscopy, CT enterography, or wireless capsule endoscopy of the small intestine. Colonic diseases are excluded with colonoscopy. CT of the abdomen is performed to look for evidence of neoplasms or lymphatic obstruction. Rarely, lymphangiography is helpful. In some situations, laparotomy with full-thickness intestinal biopsy is required to establish a diagnosis.

Treatment is directed at the underlying cause.

Elli L et al. Protein-losing enteropathy. Curr Opin Gastroenterol. 2020;36:238. [PMID: 32073507]
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DISEASES OF THE COLON & RECTUM

(See Chapter 39 **for Colorectal Cancer.)**

IRRITABLE BOWEL SYNDROME

ESSENTIALS OF DIAGNOSIS

- Chronic functional disorder characterized by abdominal pain with alterations in bowel habits.
- Symptoms usually begin in late teens to early twenties.
- Limited evaluation to exclude organic causes of symptoms.

General Considerations

IBS can be defined as an idiopathic clinical entity characterized by chronic (more than 3 months) abdominal pain that occurs in association with altered bowel habits. These symptoms may be continuous or intermittent. The 2016 Rome IV consensus definition of IBS is recurrent abdominal pain that occurs an average of at least 1 day/week and is associated with two or more of the following three features: (1) related to defecation (relief or worsening), (2) associated with a change in frequency of stool, or (3) associated with a change in form (appearance) of stool. Other symptoms supporting the diagnosis include abnormal

stool frequency; abnormal stool form (lumpy or hard; loose or watery); abnormal stool passage (straining, urgency, or feeling of incomplete evacuation); and abdominal bloating or a feeling of abdominal distention.

Patients may have other somatic or psychological complaints such as dyspepsia, heartburn, chest pain, headaches, fatigue, myalgias, urologic dysfunction, gynecologic symptoms, anxiety, or depression.

The disorder is a common problem presenting to both gastroenterologists and primary care physicians. Up to 5% of adults have symptoms compatible with the diagnosis, but most never seek medical attention. Approximately two-thirds of patients with IBS are women.

Pathogenesis

A. Abnormal Motility

A variety of abnormal myoelectrical and motor abnormalities have been identified in the colon and small intestine. In some cases, these are temporally correlated with episodes of abdominal pain or emotional stress. Differences between patients with constipation-predominant (slow intestinal transit or pelvic floor dyssynergia) and diarrhea-predominant (rapid intestinal transit, bile acid malabsorption) syndromes are reported.

B. Visceral Hypersensitivity

Patients often have a lower visceral pain threshold, reporting abdominal pain at lower volumes of colonic gas insufflation or colonic balloon inflation than controls. Many patients complain of bloating and distention, which may be due to several different factors including increased visceral sensitivity, increased gas production, impaired gas transit through the intestine, or impaired rectal expulsion. Many patients also report rectal urgency despite small rectal volumes of stool.

C. Intestinal Inflammation

It is postulated that dietary factors, medications (antibiotics), or infections may increase intestinal permeability, leading to intestinal inflammation that may contribute to alterations in intestinal motility or visceral hypersensitivity.

Symptoms compatible with IBS develop within 1 year in over 10% of patients after an episode of bacterial gastroenteritis compared with less than 2% of controls. Women and patients with antibiotic exposure or psychological stress at the onset of gastroenteritis appear to be at increased risk for developing "postinfectious" IBS.

Alterations in the intestinal microbiome composition may cause increased postprandial gas as well as bloating and distention due to degradation of undigested, fermentable carbohydrates in the small intestine or colon. A subset of patients with IBS appear to have small intestinal bacterial overgrowth. However, estimates of the proportions of patients affected vary widely in part due to the different methods used to diagnose bacterial overgrowth. In a 2020 meta-analysis of 25 studies of IBS patients who underwent testing for bacterial overgrowth, an increase in breath hydrogen or methane excretion was reported in 62% following lactulose ingestion but in 21% following glucose ingestion, and only 14% using the "gold standard" of jejunal aspirates and bacterial cultures.

D. Psychosocial Abnormalities

More than 50% of patients with irritable bowel who seek medical attention have underlying depression, anxiety, or somatization. Psychological abnormalities may influence how the patient perceives or reacts to illness and minor visceral sensations. Chronic stress may alter intestinal motility or modulate pathways that affect central and spinal processing of visceral afferent sensation.

Clinical Findings

A. Symptoms and Signs

Irritable bowel is a chronic condition. Symptoms usually begin in the late teens to twenties. The diagnosis is established in the presence of compatible symptoms and the judicious use of tests to exclude organic disease.

Abdominal pain usually is intermittent, crampy, and in the lower abdominal region. Pain is typically associated with a change in stool frequency or form and may be improved or worsened by defecation. It does not usually occur at night or interfere with sleep. Patients with IBS may be classified into one of four categories based on the predominant stool habits and stool form: IBS with diarrhea, IBS with constipation, IBS with mixed constipation and diarrhea, or IBS that is not subtyped. It is important to clarify what the patient means by these complaints. Patients with irritable bowel and constipation report infrequent bowel movements (less than three per week), hard or lumpy stools, or straining. Patients with IBS with diarrhea refer to loose or watery stools, frequent stools (more than three per day), urgency, or fecal incontinence. Many patients report that they have a firm stool in the morning followed by progressively looser movements. Complaints of visible distention and bloating are common, though these are not always clinically evident.

The patient should be asked about "alarm" symptoms that suggest a diagnosis other than IBS and warrant further investigation. The acute onset of symptoms raises the likelihood of organic disease, especially in patients older than 45 years. Nocturnal diarrhea, severe constipation or diarrhea, hematochezia, weight loss, and fever are incompatible with a diagnosis of IBS and warrant investigation for underlying disease. Patients who have a family history of cancer, IBD, or celiac disease should undergo additional evaluation. Eating habits and nutrient intake should be evaluated to screen for eating disorders.

A physical examination should be performed to look for evidence of organic disease and to allay the patient's anxieties. The physical examination usually is normal. Abdominal tenderness, especially in the lower abdomen, is common but not pronounced. A digital rectal examination should be performed in patients with constipation to screen for paradoxical anal squeezing during attempted straining that may suggest pelvic floor dyssynergia. A pelvic examination is recommended for postmenopausal women with recent onset constipation and lower abdominal pain to screen for gynecologic malignancy.

B. Laboratory Findings and Special Examinations

Although the vague nature of symptoms and patient anxiety may prompt clinicians to consider a variety of diagnostic studies, overtesting should be avoided, since the likelihood of serious organic disease is low. Nonetheless, AGA and ACG practice guidelines recommend selected laboratory tests in patients with chronic diarrhea to exclude other diagnoses. A CBC should be obtained to screen for iron deficiency anemia. A fecal calprotectin level is recommended to screen for inflammatory bowel disease; a value of greater than 50 mcg/g may warrant further endoscopic evaluation. Serologic testing for celiac disease (TG IgA) should be performed. Stool specimen examinations should be obtained in patients with increased likelihood of parasitic infection (eg, day care workers, campers, foreign travelers) for *Giardia* antigen or for multiple organisms (*Giardia*, *Cryptosporidium, Cyclospora, Entamoeba histolytica*) using nucleic acid amplification (PCR) tests. If these tests are negative, further testing is not necessary in most patients and education, reassurance, and initial empiric treatment is recommended. Routine sigmoidoscopy or colonoscopy is not recommended in patients younger than 45 years with symptoms of IBS without "alarm" symptoms but should be considered along with further laboratory testing in patients who do not improve with conservative management. In all patients aged 45 years or older who have not had a previous evaluation, colonoscopy should be obtained to exclude malignancy. When colonoscopy is performed, random mucosal biopsies should be obtained to look for evidence of microscopic colitis (which may have similar symptoms). Patients with symptoms or signs of pelvic floor disorder (dyssynergic defecation) should be referred for anorectal physiology testing (manometry and balloon expulsion test). Routine testing for bacterial overgrowth with hydrogen breath tests is not recommended.

Differential Diagnosis

A number of disorders may present with similar symptoms. Examples include colonic neoplasia, inflammatory bowel disease (ulcerative colitis, Crohn disease, microscopic colitis), bile-acid diarrhea, hyper- or hypothyroidism, parasites, malabsorption (especially celiac disease, bacterial overgrowth, lactase deficiency), causes of chronic secretory diarrhea (carcinoid), and gynecologic disorders (endometriosis, ovarian cancer). Psychiatric disorders such as depression, panic disorder, and anxiety must be considered as well. Women with refractory symptoms have an increased incidence of prior sexual and physical abuse. These diagnoses should be excluded in patients with presumed IBS who do not improve within 2–4 weeks of empiric treatment or in whom subsequent "alarm" symptoms develop.

Treatment

A. General Measures

As with other functional disorders, the most important interventions the clinician can offer are reassurance, education, and support. This includes identifying and responding to the patient's concerns, careful explanation of the pathophysiology and natural history of the disorder, setting realistic treatment goals, and involving the patient in the treatment process. Because irritable bowel symptoms are chronic, the patient's reasons for seeking consultation at this time should be determined. These may include major life events or recent psychosocial stressors, dietary or medication changes, concerns about serious underlying disease, or reduced quality of life and impairment of daily activities. In discussing with the patient the importance of the mind-gut interaction, it may be helpful to explain that alterations in visceral motility and sensitivity may be exacerbated by environmental, social, or psychological factors such as foods, medications, hormones, and stress. Symptoms such as pain, bloating, and altered bowel habits may lead to anxiety and distress, which in turn may further exacerbate bowel disturbances due to disordered communication between the gut and the CNS. Fears that the symptoms will progress, require surgery, or degenerate into serious illness should be allayed. The patient should understand that IBS is a chronic disorder characterized by periods of exacerbation and quiescence. The emphasis should be shifted from finding the cause of the symptoms to finding a way to cope with them. Moderate exercise is beneficial. Clinicians must resist the temptation to chase chronic complaints with new or repeated diagnostic studies.

B. Dietary Therapy

Patients commonly report dietary intolerances. Proposed mechanisms for dietary intolerance include food allergy, hypersensitivity, effects of gut hormones, changes in bacterial flora, increased bacterial gas production (arising in the small or large intestine), and direct chemical irritation. Fatty foods, alcohol, caffeine, spicy foods, and grains are poorly tolerated by many patients with IBS. In patients with diarrhea, bloating, and flatulence, lactose intolerance should be excluded with a hydrogen breath test or a trial of a lactose-free diet. A host of poorly absorbed, fermentable, monosaccharides and short-chain carbohydrates (FODMAPs) may exacerbate bloating, flatulence, and diarrhea in some patients. These include six food groups: fructose (corn syrups, apples, pears, honey, watermelon, raisins), lactose, fructans (garlic, onions, leeks, asparagus, artichokes), wheat-based products (breads, pasta, cereals, cakes), sorbitol (stone fruits), and raffinose (legumes, lentils, brussel sprouts, soybeans, cabbage). Dietary restriction of these fermentable carbohydrates for 2–4 weeks may improve symptoms (especially abdominal pain and bloating) in 50–65% of patients. Responders should gradually reintroduce different FODMAPs to identify food triggers. Ingestion of alpha-galactosidase supplement ("Beano") with meals containing foods with high galactoside content (eg, beans, peas, lentils, soy) may improve bowel symptoms. Gluten has not been demonstrated to increase bowel symptoms independent of other FODMAPs, and a gluten-free diet is not recommended.

Poorly fermentable soluble fiber (psyllium, oatmeal) improves global symptoms in many patients and is recommended by the 2021 American College of Gastroenterology guideline. Fermentable or insoluble fiber (bran, whole grains) may increase gas and bloating.

C. Pharmacologic Measures

More than two-thirds of patients with IBS have mild symptoms that respond readily to education, reassurance, and dietary interventions. Drug therapy should be reserved for patients with moderate to severe symptoms that do not respond to conservative measures. These agents should be viewed as being adjunctive rather than curative. Given the wide spectrum of symptoms, no single agent is expected to provide relief in all or even most patients. Nevertheless, therapy targeted at the specific dominant symptom (pain, constipation, or diarrhea) may be beneficial.

1. Antispasmodic agents—Over-the-counter, enteric-coated peppermint oil formulations (thought to relax smooth intestine) are widely available. In a 2020 randomized controlled trial, a formulation that is released in the small intestine improved abdominal pain in a higher proportion of treated patients (47%) compared with patients given placebo (34%). Based on these results and a meta-analysis of seven other randomized, controlled trials that suggested benefit, the 2021 ACG guideline has suggested that peppermint oil may be useful to relieve global IBS symptoms and abdominal pain.

Anticholinergic agents are not recommended by current guidelines due to a lack of well-designed trials demonstrating efficacy, although some practitioners continue to prescribe these agents to treat acute pain or bloating. Available agents include hyoscyamine, 0.125 mg orally (or sublingually as needed) or sustained-release, 0.037 mg or 0.75 mg orally twice daily; dicyclomine, 10–20 mg orally; or methscopolamine, 2.5–5 mg orally before meals and at bedtime. Anticholinergic side effects are common, including urinary retention, constipation, tachycardia, and dry mouth. Hence, these agents should be used with caution in older patients and in patients with constipation.

2. Antidiarrheal agents—Loperamide (2 mg orally three or four times daily) is effective for the treatment of patients with diarrhea, reducing stool frequency, liquidity, and urgency although it does not improve abdominal pain. It may best be used "prophylactically" in situations in which diarrhea is anticipated (such as stressful situations) or would be inconvenient (social engagements). Increased intracolonic bile acids due to alterations in enterohepatic circulation may contribute to diarrhea in a subset of patients with diarrhea. An empiric trial of bile salt–binding agents (cholestyramine, 2–4 g one to three times daily with meals; colesevelam, 625 mg, 1–3 tablets twice daily) may be considered. Eluxadoline (75–100 mg twice daily) is an opioid antagonist that is approved for treatment of IBS with diarrhea. In phase 3 trials, it decreased abdominal pain and improved stool consistency in approximately 25% of patients versus 16–19% with placebo; however, sphincter of Oddi dysfunction and pancreatitis developed in a small percentage (0.5%) of patients. Given its minimal efficacy, adverse side effect profile, and unproven benefit versus loperamide, further study is needed before its use can be recommended.

3. Anticonstipation agents—Treatment with oral osmotic laxatives such as polyethylene glycol 3350 (MiraLAX, 17–34 g/day) may increase stool frequency, improve stool consistency, and reduce straining but do not improve abdominal pain. Lactulose and sorbitol produce increased flatus and distention and should be avoided in patients with IBS. The secretagogues lubiprostone (8 mcg orally twice daily), linaclotide (290 mcg orally once daily), and plecanatide (3 mg orally once daily) are FDA approved for treatment of IBS with constipation based on modest demonstrated efficacy and are recommended in the 2021 ACG guideline. Through different mechanisms, these agents stimulate increased intestinal chloride and fluid secretion, resulting in accelerated colonic transit. In clinical trials, lubiprostone led to global symptom improvement in 18% of patients compared with 10% of patients who received placebo (a therapeutic gain of 8%). Using different FDA-approved endpoints for significant clinical response (30% reduction in abdominal pain and more than three spontaneous bowel movements per week), phase 3 trials of linaclotide and plecanatide have demonstrated similar therapeutic gains: linaclotide 12.5% versus placebo 4% and plecanatide 26% versus placebo 16%. Tegaserod is a 5-HT_4-receptor agonist that stimulates peristalsis. After original approval in 2002, it was voluntarily withdrawn from the market in 2007 because of cardiovascular safety concerns. Tegaserod (6 mg orally twice daily) was reapproved by the FDA in 2019 for women under age 65 with IBS and constipation after evaluation of clinical and safety data from 29 placebo-controlled trials and newer treatment outcome data. It may be considered for treatment of women age younger than 65 years with one or fewer cardiovascular risk factors whose IBS with constipation has not improved with secretagogue therapy. Patients with intractable constipation should undergo further assessment for slow colonic transit and pelvic floor dysfunction (see Constipation, above).

4. Psychotropic agents—Patients with predominant symptoms of pain or bloating may benefit from low doses of tricyclic antidepressants, which are believed to have effects on motility, visceral sensitivity, and central pain perception that are independent of their psychotropic effects. Because of their anticholinergic effects, these agents may be more useful in patients with diarrhea-predominant than constipation-predominant symptoms. Oral nortriptyline, desipramine, or imipramine may be started at a low dosage of 10 mg at bedtime and increased gradually to 50–150 mg as tolerated. Response rates do not correlate with dosage, and many patients respond to doses of 50 mg or less daily. Side effects are common, and lack of efficacy with one agent does not preclude benefit from another. Agents with higher anticholinergic activity may improve diarrhea but worsen constipation. Improvement should be evident within 4 weeks. The oral SSRIs (sertraline, 25–100 mg daily; citalopram, 10–20 mg; paroxetine, 20–50 mg daily; or fluoxetine, 10–40 mg daily) may be used to treat irritable bowel symptoms as well as treat mood disorders. SSRIs may accelerate GI transit and improve constipation. Anxiolytics should not be used chronically in IBS because of their habituation potential. Patients with major depression or anxiety disorders should be identified and treated with therapeutic doses of appropriate agents.

5. Serotonin receptor antagonists—Alosetron is a 5-HT_3 antagonist that is FDA approved for the treatment of women with severe IBS with predominant diarrhea. Unfortunately, due to cases of severe constipation and a small (1:1000) but significant risk of ischemic colitis, alosetron is restricted to women with severe IBS with diarrhea who have not responded to conventional therapies and who have been educated about the relative risks and benefits of the agent. A randomized crossover trial of another 5-HT_3 antagonist, ondansetron 4–8 mg three times daily, showed overall superior symptom improvement, including stool frequency, consistency, and urgency. At this time, 5-HT_3 antagonists may be considered after careful discussion of the risks and benefits in carefully selected patients with severe diarrhea-predominant IBS.

6. Nonabsorbable antibiotics—Rifaximin (550 mg, three times daily for 14 days) may be considered in patients with refractory symptoms, especially bloating. A 2012 meta-analysis identified a 9.9% greater improvement in bloating with rifaximin compared with placebo, a modest gain that is similar to other less expensive therapies. Symptom improvement may be attributable to suppression of bacteria in either the small intestine or colon, resulting in decreased bacterial carbohydrate fermentation, diarrhea, and bloating.

7. Probiotics—Meta-analyses of small controlled clinical trials of probiotics report improved symptoms of pain, bloating, and flatulence in some patients; however, there is no proven benefit. Probiotics are not recommended for IBS treatment in the 2020 AGA and 2021 ACG guidelines.

D. Psychological Therapies

Cognitive-behavioral therapies, relaxation techniques, yoga, and hypnotherapy appear to be beneficial in some patients. Patients with underlying psychological abnormalities may benefit from evaluation by a psychiatrist or psychologist. Patients with severe disability should be referred to a pain management center.

Prognosis

Most patients with IBS learn to cope with their symptoms and lead productive lives.

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ANTIBIOTIC-ASSOCIATED COLITIS

ESSENTIALS OF DIAGNOSIS

- Most cases of antibiotic-associated diarrhea are not attributable to *C difficile* and are usually mild and self-limited.
- Symptoms of antibiotic-associated colitis vary from mild to fulminant; almost all colitis is attributable to *C difficile*.
- Diagnosis in most cases established by stool assay.

General Considerations

Antibiotic-associated diarrhea is a common clinical occurrence. Characteristically, the diarrhea occurs during the period of antibiotic exposure, is dose related, and resolves spontaneously after discontinuation of the antibiotic. In most cases, this diarrhea is mild, self-limited, and does not require any specific laboratory evaluation or treatment. Stool examination usually reveals no fecal leukocytes, and stool cultures reveal no pathogens. Although *C difficile* is identified in the stool of 15–25% of cases of antibiotic-associated diarrhea, it is also identified in 5–10% of patients treated with antibiotics who do not have diarrhea. Most cases of antibiotic-associated diarrhea are due to changes in colonic bacterial fermentation of carbohydrates and are not due to *C difficile.*

Antibiotic-associated colitis is a significant clinical problem almost always caused by *C difficile* infection that colonizes the colon and releases two toxins: TcdA and TcdB. Found throughout hospitals in patient rooms and bathrooms, *C difficile* is readily transmitted from patient to patient by hospital personnel. Fastidious hand washing and use of disposable gloves are helpful in minimizing transmission and reducing infections in hospitalized patients. In hospitalized patients, *C difficile* colitis occurs in approximately 20% of those who are colonized at admission and 3.5% of those not colonized. In both hospital-associated and community infections, most episodes of colitis occur in people who have received antibiotics that disrupt the normal bowel flora and thus allow the bacteria to flourish. Although almost all antibiotics have been implicated, colitis most commonly develops after use of ampicillin, clindamycin, third-generation cephalosporins, and fluoroquinolones. Symptoms usually begin during or shortly after antibiotic therapy but may be delayed for up to 8 weeks. All patients with acute diarrhea should be asked about recent antibiotic exposure. Patients who are older; debilitated; immunocompromised; receiving multiple antibiotics or prolonged (more than 10 days) antibiotic therapy; receiving enteral tube feedings, PPIs, or chemotherapy; or who have IBD have a higher risk of acquiring *C difficile* and developing *C difficile*–associated diarrhea.

Pathogenic strains of *C difficile* produce two toxins: toxin TcdA is an enterotoxin and toxin TcdB is a cytotoxin. A more virulent strain of *C difficile* (NAP1) that contains

an 18-base pair deletion of the TcdC inhibitory gene results in higher toxin A and B production. This hypervirulent strain is more prevalent among hospital-associated infections and associated with outbreaks of severe disease but now appears to be declining in incidence.

Clinical Findings

A. Symptoms and Signs

Most patients report mild to moderate greenish, foul-smelling watery diarrhea 3–15 times per day with lower abdominal cramps. Physical examination is normal or reveals mild left lower quadrant tenderness. The stools may have mucus but seldom gross blood. Over half of hospitalized patients diagnosed with *C difficile* colitis have severe disease as defined by a white blood count greater than 15,000/mcL (15×10^9/L) or serum creatinine greater than 1.5 g/dL. Fever is uncommon.

Fulminant disease occurs in up to 10% of patients. It is characterized by hypotension or shock, ileus, or megacolon. Most patients have abdominal pain or tenderness, distention, and profuse diarrhea; however, diarrhea may be absent or appear to be improving in patients with ileus. Laboratory data suggestive of severe disease include a WBC greater than 30,000/mcL (30×10^9/L), serum albumin less than 2.5 g/dL (due to protein-losing enteropathy), elevated serum lactate, and rising serum creatinine.

B. Special Examinations

1. Stool studies—Stool testing for *C difficile* is recommended in hospitalized patients with dysentery or three or more liquid stools within 24 hours or outpatients with diarrhea persisting longer than 1 week. Three types of diagnostic tests are in common use: (1) an immunoassay for glutamate dehydrogenase (GDH) protein has high sensitivity and negative predictive value (95%) for the detection of toxigenic and nontoxigenic *C difficile,* though it does not distinguish active infection with toxin secretion from colonization; (2) PCR tests amplify the *C difficile* toxin gene (usually *TcdB*); they have extremely high sensitivity (97–99%) for detection of *C difficile* as well as the ability to detect the hypervirulent NAP1 strain but like the GDH assay cannot distinguish active infection from colonization; (3) rapid enzyme immunoassays (EIAs) detect the presence of *C difficile*–toxins TcdA and TcdB with 75–95% sensitivity, confirming active toxin-secreting infection. As the initial diagnostic test, most laboratories screen for *C difficile* with either the PCR toxin gene test or the GDH protein assay. A negative PCR or GDH assay effectively excludes infection. Treatment based on PCR or GDH testing alone may result in unnecessary treatment of patients with *C difficile* colonization. Therefore, laboratories may perform secondary testing with toxin EIA to distinguish colonization from active toxin-producing infection.

2. Flexible sigmoidoscopy—Flexible sigmoidoscopy is not needed in patients who have typical symptoms and a positive stool test. It may clarify the diagnosis in patients with positive *C difficile* toxin assays who have atypical symptoms or who have persistent diarrhea despite appropriate therapy. In patients with mild to moderate symptoms, there may be no abnormalities or only patchy or diffuse, nonspecific colitis indistinguishable from other causes. In patients with severe illness, true **pseudomembranous colitis** is seen.

3. Imaging studies—Abdominal radiographs or noncontrast abdominal CTs are obtained in patients with severe or fulminant symptoms to look for evidence of colonic dilation and wall thickening. Abdominal CT also is useful in the evaluation of hospitalized patients with abdominal pain or ileus without significant diarrhea, in whom the presence of colonic wall thickening suggests unsuspected *C difficile* colitis. CT is also useful in the detection of possible perforation.

Differential Diagnosis

In the hospitalized patient in whom acute diarrhea develops after admission, the differential diagnosis includes simple antibiotic-associated diarrhea (not related to *C difficile*), enteral feedings, medications, and ischemic colitis. Other infectious causes are unusual in hospitalized patients in whom diarrhea develops more than 72 hours after admission, and it is not cost-effective to obtain stool cultures unless tests for *C difficile* are negative. *Klebsiella oxytoca* may cause a distinct form of antibiotic-associated hemorrhagic colitis that is segmental (usually in the right or transverse colon); spares the rectum; and is more common in younger, healthier outpatients.

Complications

Severe colitis may progress quickly to fulminant disease, resulting in hemodynamic instability, respiratory failure, metabolic acidosis, megacolon (more than 7-cm diameter), perforation, and death. Chronic untreated colitis may result in weight loss and protein-losing enteropathy.

Treatment

A. Initial Treatment

To reduce transmission within health care facilities, patients with suspected or proven *C difficile* infection should be placed on strict contact precautions and health care workers should apply careful handwashing before and after contact. If possible, therapy with the inciting antibiotic should be discontinued as soon as possible. The treatment of an initial episode of *C difficile* colitis is determined by the severity of disease. For patients with nonsevere disease, oral fidaxomicin (200 mg orally two times daily) and vancomycin (125 mg orally four times daily) are equally effective for initial treatment, but recurrence rates are lower with fidaxomicin than vancomycin (15% vs 25%). Fidaxomicin may be preferred as first-line treatment for patients believed to be at higher risk for recurrent disease. Recommended treatment duration is 10 days in most situations but is extended in patients requiring prolonged antibiotic therapy for other infections. Metronidazole (500 mg orally three times daily) is no longer recommended for initial therapy except in mild disease when vancomycin or

fidaxomicin is unavailable. Symptomatic improvement occurs in most patients within 72 hours. Following treatment, stool assays may remain positive for several weeks after symptom resolution.

For patients with fulminant disease, vancomycin 500 mg orally four times daily along with metronidazole 500 mg intravenously every 8 hours are recommended. In patients with ileus, vancomycin may be administered by nasoenteric tube and by rectal enema (500 mg in 100 mL normal saline by enema every 6 hours). The efficacy of fidaxomicin for severe or fulminant disease requires further investigation. Early surgical consultation is recommended for all patients with severe or fulminant disease. Total abdominal colectomy or loop ileostomy with colonic lavage may be required in patients with toxic megacolon, perforation, sepsis, or hemorrhage. Poor surgical candidates should be considered for **fecal microbiota transplantation (FMT)** administered by colonoscopy at 3- to 5-day intervals (see below).

B. Treatment of Relapse

Up to 20% of patients have a relapse of diarrhea from *C difficile* within 8 weeks after stopping initial therapy. This may be due to reinfection or failure to eradicate the organism. Guidelines recommend that the first recurrence be treated with fidaxomicin 200 mg orally twice daily for 10 days or with a prolonged tapering regimen of vancomycin 125 mg orally four times daily for 14 days; twice daily for 7 days; once daily for 7 days; then every other 2 or 3 days for 2–8 weeks. Second recurrence should be treated with an additional vancomycin tapering regimen, as above.

For patients with two or more relapses, guidelines recommend consideration of FMT, in which a suspension of fecal bacteria from a healthy donor is given to the patient with infection. Fecal specimens that have been screened for infectious agents are commercially available. The fecal microbiota usually is instilled into the patient by one of two methods: infusion through a colonoscope into the terminal ileum and colon or ingestion of multiple freeze-dried capsules. Meta-analysis of 34 studies of FMT for recurrent or refractory *C difficile* suggests that efficacy is somewhat higher following colonoscopic administration (92–94%) than oral administration (74–96%); however, the oral capsule method may be preferred for non-hospitalized patients due to relative ease of administration. Randomized studies have demonstrated significantly higher resolution of *C difficile* diarrhea with FMT (92–94%) than with vancomycin (19–31%) or fidaxomicin (42%). FMT carries the potential risk of transmission of serious, even sometimes fatal, infection. However, with proper screening and stool testing of donors, the risk of such infection appears to be low.

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INFLAMMATORY BOWEL DISEASE

The term "inflammatory bowel disease" includes ulcerative colitis and Crohn disease. The diagnosis and management of each will be reviewed in the sections below. In the United States, there are approximately 1.6 million people with IBD with adjusted annual incidences of 12.2 cases/100,000 person-years for ulcerative colitis and 10.7 cases/100,000 person-years for Crohn disease. These diseases can occur at any age but most commonly begin in adolescents and adults under age 40 years. The natural history of both varies from mild, often intermittent disease symptoms to severe disease characterized by elevated inflammatory markers and mucosal ulcerations that may lead to intestinal complications (bleeding, strictures, fistulas, surgery), nutritional deficiencies, and impaired quality of life. Both diseases may be associated with several extraintestinal manifestations, including oral ulcers, oligoarticular or polyarticular nondeforming peripheral arthritis, spondylitis or sacroiliitis, episcleritis or uveitis, erythema nodosum, pyoderma gangrenosum, hepatitis and sclerosing cholangitis, and thromboembolic events.

Pharmacologic Therapy

Although ulcerative colitis and Crohn disease appear to be distinct entities, several pharmacologic agents are used to treat both. Despite extensive research, there are still no specific therapies for these diseases. The mainstays of therapy are 5-aminosalicylic acid derivatives, corticosteroids, immunomodulating drugs (such as mercaptopurine or azathioprine and methotrexate) and other small-molecule agents, and biologic therapies.

A. 5-Aminosalicylic Acid (5-ASA)

5-ASA is a topically active agent that has a variety of anti-inflammatory effects. It is readily absorbed from the small intestine but demonstrates minimal colonic absorption. Several oral and topical compounds have been designed to target delivery of 5-ASA to the colon or distal small intestine.

1. Oral formulations—Mesalamine compounds are oral 5-ASA formulations that are either coated in various pH-sensitive resins (Asacol, Apriso, and Lialda) that release 5-ASA throughout the colon or packaged in timed-release capsules (Pentasa) that release 5-ASA in the small intestine and colon. Side effects of these compounds are uncommon but include nausea, rash, diarrhea, pancreatitis, and acute interstitial nephritis. Sulfasalazine and balsalazide are two oral formulations that contain 5-ASA linked by an azo bond to another agent (sulfapyridine or an inert peptide, respectively) in order to prevent small intestine absorption. Following cleavage of the azo bond by colonic bacteria, 5-ASA is released in the colon. The sulfapyridine group is absorbed

and may cause side effects in 15–30% of patients, including nausea, oligospermia, leukopenia, agranulocytosis, impaired folate metabolism, and hypersensitivity (fever, rash, hemolytic anemia, pneumonitis). Because of its side effects, sulfasalazine is used less frequently than balsalazide and other 5-ASA agents.

2. Topical mesalamine—5-ASA is provided in the form of suppositories (Canasa; 1000 mg) and enemas (Rowasa; 4 g/60 mL). These formulations can deliver much higher concentrations of 5-ASA to the distal colon than oral compounds. Side effects are uncommon.

B. Corticosteroids

A variety of intravenous, oral, and topical corticosteroid formulations have been used in inflammatory bowel disease. They have utility in the short-term treatment of moderate to severe disease. However, long-term use is associated with serious, potentially irreversible side effects and is to be avoided. The agents, route of administration, duration of use, and tapering regimens used are based more on personal bias and experience than on data from rigorous clinical trials. In hospitalized adult patients with severe disease, current guidelines recommend intravenous methylprednisolone 40–60 mg/day, which may be given in single or divided doses. Oral formulations are prednisone or methylprednisolone. Budesonide is an oral corticosteroid with high topical anti-inflammatory activity but low systemic activity due to high first-pass hepatic metabolism. An enteric-coated formulation is available (Entocort) that targets delivery to the terminal ileum and proximal colon. An enteric coated, multi-matrix, delayed-release formulation (budesonide Multi Matrix [MMX] formulation [Uceris]) is available that releases budesonide throughout the colon. Topical preparations are provided as hydrocortisone suppositories (25 mg and 30 mg), foam (10%, 80 mg), and enemas (100 mg) and as budesonide foam (2 mg).

C. Immunomodulating Drugs and Other Small Molecules

1. Thiopurines (mercaptopurine and azathioprine)—In current clinical practice, these drugs are mainly used in combination with anti-TNF agents (see section D.1. below) in patients with moderate to severe Crohn disease and ulcerative colitis to reduce antibody formation against the biologic agent and to increase the likelihood of clinical remission through increased anti-TNF drug levels and possible synergistic effects. In some settings, they continue to be used as monotherapy to maintain remission in patients with quiescent disease. Side effects of mercaptopurine and azathioprine, including allergic reactions (fever, rash, or arthralgias) and nonallergic reactions (nausea, vomiting, pancreatitis, hepatotoxicity, bone marrow suppression, infections), occur in 15% of patients. Thiopurines are associated with up to a 2.5-fold increased risk of non-Hodgkin lymphomas (0.5/1000 patient-years). The risk rises after 1–2 years of exposure and is higher in men younger than age 30 years and patients older than age 50 years. Thiopurines also are associated with a risk of human papillomavirus (HPV)–related cervical dysplasia and with an increased risk of non-melanoma skin cancer. Younger patients also are at risk for severe primary Epstein-Barr virus (EBV) infection, if not previously exposed.

About 1 person in 300 has a homozygous mutation of one of the enzymes that metabolizes thiopurine methyltransferase (TPMT), placing them at risk for profound immunosuppression; 1 person in 9 is heterozygous for TPMT, resulting in intermediate enzyme activity. Measurement of TPMT functional activity is recommended prior to initiation of therapy. Treatment should be withheld in patients with absent TPMT activity. The most effective dose of mercaptopurine is 1–1.5 mg/kg and for azathioprine, is 2–3 mg/kg daily. For patients with normal TPMT activity, both drugs may be initiated at the weight-calculated dose. A CBC should be obtained weekly for 4 weeks, biweekly for 4 weeks, and then every 1–3 months for the duration of therapy. Liver biochemical tests should be measured periodically. Some clinicians prefer gradual dose escalation, especially for patients with intermediate TPMT activity or for whom TPMT measurement is not available; both drugs may be started at 25 mg/day and increased by 25 mg every 1–2 weeks while monitoring for myelosuppression until the target dose is reached. If the white blood count falls below 4000/mcL (4.0×10^9/L) or the platelet count falls below 100,000/mcL (100×10^9/L), the medication should be held for at least 1 week before reducing the daily dose by 25–50 mg. Measurement of thiopurine metabolites (6-TG and 6-MMP) is of unproved value in most patients but is recommended in patients who have not responded to standard, weight-based dosing or in whom adverse effects develop.

2. Methotrexate—Low-dose oral methotrexate (12.5 mg once weekly) is used in combination with anti-TNF agents to prevent immunogenicity. Methotrexate is an analog of dihydrofolic acid. Side effects of methotrexate include nausea, vomiting, stomatitis, infections, bone marrow suppression, hepatic fibrosis, and life-threatening pneumonitis. A CBC and liver chemistries should be monitored every 3 months. Folate supplementation (1 mg/day) should be administered. Because methotrexate is teratogenic, it should be discontinued in men and women at least 6 months before conception and during pregnancy.

3. Janus kinase inhibitors—Tofacitinib is a nonbiologic small-molecule inhibitor of Janus kinase (JAK 1/3), which is involved through the JAK-STAT pathway in modulation of multiple interleukins. It is currently approved by the FDA as second-line therapy for the treatment of moderate to severe ulcerative colitis (not Crohn disease) that has not responded to anti-TNF therapy. It has rapid oral absorption and lacks immunogenicity. The FDA has issued a black box warning about an increased risk of blood clots and deaths in rheumatoid arthritis patients taking tofacitinib 10 mg orally twice daily compared with patients taking 5 mg orally twice daily of anti-TNF agents. Tofacitinib should not be prescribed to patients deemed at higher risk for thrombosis. It has a low risk of adverse events, including infections, with the exception of herpes zoster (it occurs in up to 5% of patients). Prior to initiating treatment, patients without a history of varicella vaccination

should undergo testing for varicella antibodies and receive varicella vaccination if antibody negative. Vaccination with inactivated (not live) recombinant zoster (Shingrix) is recommended in all patients without confirmed varicella vaccination or prior varicella infection.

4. Sphingosine 1-phosphate receptor modulators—Ozanimod is an oral agent that binds to lymphocyte sphingosine 1-phosphate receptors (types 1 and 5), thereby blocking their ability to leave lymph nodes. It is currently approved for the treatment of moderate to severe ulcerative colitis. It leads to a mean 45% reduction of peripheral lymphocyte count that may last for up to 2 weeks after drug discontinuation. Liver chemistries and CBC should be obtained 3–6 months after drug initiation. Severe lymphopenia less than 200×10^9/L (less than 0.2×10^9/L) should prompt drug dosage reduction or discontinuation. The risk of serious adverse events from ozanimod is low but includes hypertension, bradyarrhythmia, liver transaminase elevation, and macular edema. Herpes simplex reactivation (1.3%) or herpes zoster (2.2%) may occur. Prior to initiation of therapy, patients without a history of varicella vaccination should undergo testing for varicella antibodies and, if antibody negative, be given inactivated recombinant zoster (Shingrix) vaccine (see Immunizations below).

D. Biologic Therapies

A number of biologic therapies are available or in clinical testing that target various components of the immune system. Biologic agents are highly effective for patients with moderate to severe disease and when administered early in the disease course may improve the natural history of disease. The potential benefits of these agents must be weighed with their high cost and risk of rare but serious and potentially life-threatening side effects.

1. Anti-TNF therapies—Four monoclonal antibodies to TNF currently are available for the treatment of inflammatory bowel disease: infliximab, adalimumab, golimumab, and certolizumab. All four agents bind and neutralize soluble as well as membrane-bound TNF on macrophages and activated T lymphocytes, thereby preventing TNF stimulation of effector cells.

Infliximab is a chimeric (75% human/25% mouse) IgG_1 antibody that is administered by intravenous infusion. A three-dose regimen of 5 mg/kg administered at 0, 2, and 6 weeks is recommended for acute induction, followed by infusions every 8 weeks for maintenance therapy. Acute infusion reactions occur in 5–10% of infusions but are uncommon in patients receiving regularly scheduled infusions or concomitant immunomodulators (ie, azathioprine or methotrexate). Most reactions are mild and can be treated by slowing the infusion rate and administering acetaminophen and diphenhydramine. Severe reactions (hypotension, severe shortness of breath, rigors, severe chest discomfort) occur in less than 1% and may require oxygen, diphenhydramine, hydrocortisone, and epinephrine. With repeated, intermittent intravenous injections, antibodies to infliximab develop in up to 40% of patients, which are associated with a shortened duration or loss of response and increased risk of acute or delayed infusion reactions. Giving infliximab in a regularly scheduled maintenance therapy (eg, every 8 weeks) or in combination with other immunomodulating agents (azathioprine, mercaptopurine, or methotrexate) significantly reduces the development of antibodies to less than 10%.

Adalimumab and golimumab are fully human IgG_1 antibodies that are administered by subcutaneous injection. For adalimumab, a dose of 160 mg at week 0 and 80 mg at week 2 is recommended for acute induction, followed by maintenance therapy with 40 mg subcutaneously every other week. For golimumab, a dose of 200 mg at week 0 and 100 mg at week 2 is recommended for acute induction, followed by maintenance therapy with 100 mg subcutaneously every 4 weeks.

Certolizumab is a fusion compound in which the Fab1 portion of a chimeric (95% human/5% mouse) TNF-antibody is bound to polyethylene glycol in order to prolong the drug half-life. However, certolizumab is infrequently used due to lower clinical efficacy.

Hypersensitivity reactions are rare with subcutaneous anti-TNF therapies. Antibodies to adalimumab or golimumab develop in 5% of patients and to certolizumab in 10%, which may lead to shortened duration or loss of response to the drug.

Serious infections with anti-TNF therapies may occur in 2–5% of patients, including sepsis, pneumonia, abscess, and cellulitis; however, controlled studies suggest the increased risk may be attributable to increased severity of disease and concomitant use of corticosteroids or immunomodulators. Patients treated with anti-TNF therapies are at increased risk for the development of opportunistic infections with intracellular bacterial pathogens including tuberculosis, mycoses (candidiasis, histoplasmosis, coccidioidomycosis, nocardiosis), and listeriosis, and with reactivation of viral infections, including hepatitis B, herpes simplex, varicella zoster, and EBV. Prior to use of these agents, patients should be screened for latent tuberculosis with PPD testing and a chest radiograph. Antinuclear and anti-DNA antibodies occur in a large percentage of patients; however, the development of drug-induced lupus is rare. All agents may cause severe hepatic reactions leading to acute hepatic failure; liver biochemical tests should be monitored routinely during therapy. Anti-TNF therapies may increase the risk of skin cancer, hence annual dermatologic examinations are recommended. There may be a small risk of non-Hodgkin lymphoma in patients taking anti-TNF monotherapy; however, the risk is much higher in patients receiving a combination of anti-TNF and a thiopurine (6.1-fold increase; 0.95/1000 person-years). Rare cases of optic neuritis and demyelinating diseases, including multiple sclerosis have been reported. Anti-TNF therapies may worsen heart failure in patients with cardiac disease.

In patients with active inflammatory bowel disease, monitoring of anti-TNF trough levels and any anti-drug antibodies is useful to optimize drug levels and guide therapy. Therapeutic drug monitoring is indicated in patients who have poor clinical response or who have lost clinical response. Patients with high titers of anti-drug

antibodies should be switched to a different anti-TNF agent. Anti-TNF therapy is considered to have failed when patients have a poor response despite adequate anti-TNF trough concentrations; another class of drugs should be tried. Increasingly, experts recommend proactive measurement of drug and antibody concentrations in all patients to optimize clinical response and minimize drug antibody formation (more common at low drug levels). At present, recommended trough concentrations during maintenance therapy are greater than 7 mcg/mL for infliximab, greater than 7–10 mcg/mL for adalimumab, and greater than 1 mcg/mL for golimumab.

2. Anti-integrins—Anti-integrins decrease the trafficking of circulating leukocytes through the vasculature, reducing chronic inflammation. Vedolizumab is FDA approved for patients with moderately active ulcerative colitis or Crohn disease who have an inadequate response to or intolerance of corticosteroids, immunomodulators, or anti-TNF agents. Induction therapy is given as a 300-mg intravenous dose at weeks 0, 2, and 6. This is followed by maintenance therapy of 300 mg intravenously every 4–8 weeks based on clinical response or serum trough concentrations. Thus far, vedolizumab does not appear to be associated with an increased risk of serious infections or malignancy. Infusion reactions are uncommon. Antibodies develop in 3.7% but may not interfere with drug efficacy. Combination therapy with immunomodulators does not appear to increase rates of clinical response or remission. Therapeutic drug monitoring is of uncertain utility.

3. Anti-IL-12/23 antibody—Ustekinumab is a human IgG_1 monoclonal antibody that binds the p40 subunit of IL-12 and IL-23, interfering with their receptor binding on T cells, NK cells, and antigen presenting cells. Ustekinumab is FDA approved for the treatment of patients with moderate to severe Crohn disease and for those with moderate to severe ulcerative colitis. Induction therapy is given as a single, weight-based intravenous dose (approximately 5–7 mg/kg), followed by 90 mg every 8 weeks by subcutaneous injection. There has been no demonstrated increase in severe infections or malignancy, and other serious events are rare. Antibodies to ustekinumab develop in less than 2.3% of patients and their impact on treatment efficacy is uncertain. Combination therapy with immunomodulators does not appear to increase rates of clinical response or remission. Therapeutic drug monitoring is of uncertain utility.

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Immunizations

Due to increased risk of vaccine-preventable infections, vaccination status should be confirmed in ***all*** patients with IBD. Inactivated vaccines—hepatitis A and B, recombinant herpes zoster (Shingrix), influenza, and DTaP (tetanus, diphtheria, pertussis) vaccines—may be safely administered in patients receiving immunosuppressive agents; however, efficacy may be attenuated. Pneumococcal vaccine is recommended for patients who are over age 65 or who are receiving immunosuppressive agents. Live virus vaccines (varicella; measles, mumps, rubella) should considered ***before*** initiating immunosuppressives for previously unvaccinated patients who lack serologic evidence of prior infection. Live virus vaccines should ***not*** be administered to patients taking immunosuppressive agents.

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Lifestyle & Social Support for Patients

IBD is a lifelong illness that can have profound physical, psychological, and social impacts on the individual and their family. A therapeutic relationship between the patient and clinician that involves trust, open communication, and shared decision-making is critical to achieving optimal outcomes. Adherence to a healthy lifestyle is associated with improved outcomes, including reduced mortality. Patients may be encouraged to stop or avoid smoking, maintain light alcohol consumption, and engage in moderate to vigorous physical activity. Diets that are low in saturated fats and red meats and high in fruits, vegetables (including the Mediterranean diet) may be encouraged in patients without intestinal strictures. Patients should be screened for anxiety and depression, and psychological support (including cognitive behavioral therapy) offered when appropriate. Patients should be encouraged to become involved in the Crohn's and Colitis Foundation of America (CCFA) for patient-centered educational materials and local support groups (https://www.crohnscolitisfoundation.org/).

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1. Crohn Disease

ESSENTIALS OF DIAGNOSIS

- Insidious onset.
- Intermittent bouts of low-grade fever, diarrhea, and right lower quadrant pain.
- Right lower quadrant mass and tenderness.
- Perianal disease with abscess, fistulas.
- Radiographic or endoscopic evidence of ulceration, stricturing, or fistulas of the small intestine or colon.

General Considerations

One-third of cases of Crohn disease involve the small bowel only, most commonly the terminal ileum (ileitis). Half of all cases involve the small bowel and colon, most often the terminal ileum and adjacent proximal ascending colon (ileocolitis). In 20% of cases, the colon alone is affected. One-third of patients have associated perianal disease (fistulas, fissures, abscesses). Less than 5% of patients have symptomatic involvement of the upper intestinal tract. Unlike ulcerative colitis, Crohn disease is a *transmural* process that may involve *any* segment of the GI tract. It results in mucosal inflammation and ulceration, stricturing, fistula development, and abscess formation. Cigarette smoking is strongly associated with the development of Crohn disease, resistance to medical therapy, and early disease relapse.

Clinical Findings

A. Symptoms and Signs

Because of the variable location of involvement and severity of inflammation, Crohn disease may present with a variety of symptoms and signs. In eliciting the history, the clinician should take particular note of fevers, weight loss, abdominal pain, number of liquid bowel movements per day, general sense of well-being, and prior surgical resections. Physical examination should focus on the patient's temperature, weight, and nutritional status, abdominal tenderness or mass, rectal examination, and extraintestinal manifestations. Approximately 20–30% of patients have an indolent, nonprogressive course. The majority will require specific therapies (often biologic agents) to reduce inflammation, improve quality of life, and reduce the risk of surgery and hospitalization. Most commonly, there is one or a combination of the following clinical constellations.

1. Luminal inflammatory disease—This is the most common presentation at diagnosis (60–80%). Patients report malaise, weight loss, and loss of energy. In patients with ileitis or ileocolitis, there may be diarrhea, usually nonbloody and often intermittent. In patients with colitis involving the rectum or left colon, there may be bloody diarrhea and fecal urgency, mimicking the symptoms of ulcerative colitis. Cramping or steady right lower quadrant or periumbilical pain is common. Physical examination reveals focal tenderness, usually in the right lower quadrant. A palpable, tender mass that represents thickened or matted loops of inflamed intestine may be present in the lower abdomen.

2. Intestinal stricturing—Narrowing of the small bowel may occur as a result of inflammation or fibrotic stenosis. Patients report postprandial bloating, cramping pains, and loud borborygmi. This may occur in patients with active inflammatory symptoms or later in the disease from chronic fibrosis without other systemic symptoms or signs of inflammation.

3. Penetrating disease and fistulae—Sinus tracts that penetrate through the bowel, where they may be contained or form fistulas to adjacent structures, develop in a subset of patients. Penetration through the bowel can result in an intra-abdominal or retroperitoneal phlegmon or abscess manifested by fevers, chills, a tender abdominal mass, and leukocytosis. Fistulas between the small intestine and colon commonly are asymptomatic, but can result in diarrhea, weight loss, bacterial overgrowth, and malnutrition. Fistulas to the bladder produce recurrent infections. Fistulas to the vagina result in malodorous drainage and problems with personal hygiene. Fistulas to the skin usually occur at the site of surgical scars.

4. Perianal disease—One-third of patients with either large or small bowel involvement develop perianal disease manifested by large painful skin tags, anal fissures, perianal abscesses, and fistulas.

5. Extraintestinal manifestations—Extraintestinal manifestations may include arthralgias, arthritis, iritis or uveitis, pyoderma gangrenosum, or erythema nodosum. Oral aphthous lesions are common.

B. Laboratory Findings

Laboratory values may reflect inflammatory activity or nutritional complications of disease. A CBC and serum albumin should be obtained in all patients. Anemia may reflect chronic inflammation, mucosal blood loss, iron deficiency, or vitamin B_{12} malabsorption secondary to terminal ileal inflammation or resection. Leukocytosis may reflect inflammation or abscess formation or may be secondary to corticosteroid therapy. Hypoalbuminemia may be due to intestinal protein loss, malabsorption, bacterial overgrowth, or chronic inflammation. The ESR or CRP level is elevated in many patients during active inflammation; however, one-third have a normal CRP level. Fecal calprotectin is an excellent noninvasive test. Elevated levels are correlated with active inflammation as demonstrated by ileocolonoscopy or radiologic CT or MR enterography. Stool specimens are sent for examination for routine pathogens and *C difficile* toxin by microscopy, culture, and toxin assay or by rapid multiplex PCR diagnostic assessment.

C. Special Diagnostic Studies

In most patients, the initial diagnosis of Crohn disease is based on a compatible clinical picture with supporting

endoscopic, pathologic, and radiographic findings. Colonoscopy usually is performed first to evaluate the colon and terminal ileum and to obtain mucosal biopsies. Typical endoscopic findings include aphthoid, linear or stellate ulcers, strictures, and segmental involvement with areas of normal-appearing mucosa adjacent to inflamed mucosa. Large or deep mucosal ulcers portend a higher risk for progressive disease. In 10% of cases, it may be difficult to distinguish ulcerative colitis from Crohn disease. Granulomas on biopsy are present in less than 25% of patients but are highly suggestive of Crohn disease. CT or MR enterography is obtained in patients with suspected small bowel involvement. Suggestive findings include ulcerations, strictures, and fistulas; in addition, CT or MR enterography may identify bowel wall thickening and vascularity, mucosal enhancement, and fat stranding. MR enterography, where available, may be preferred due its lack of radiation exposure. Capsule imaging may help establish a diagnosis when clinical suspicion for small bowel involvement is high but radiographs are normal or nondiagnostic. Barium upper GI series with small bowel follow through should no longer be performed.

Complications

A. Abscess

The presence of a tender abdominal mass with fever and leukocytosis suggests an abscess. Emergent CT or MR of the abdomen is necessary to confirm the diagnosis. Patients should be given broad-spectrum antibiotics. Smaller abscesses (less than 3 cm) respond to antibiotic therapy but larger abscesses usually require percutaneous or surgical drainage.

B. Obstruction

Small bowel obstruction may develop secondary to active inflammation or chronic fibrotic stricturing and is often acutely precipitated by dietary indiscretion. Patients should be given intravenous fluids with nasogastric suction. Systemic corticosteroids are indicated in patients with symptoms or signs of active inflammation but are unhelpful in patients with inactive, fixed disease. Patients unimproved on medical management require surgical resection of the stenotic area or stricturoplasty.

C. Abdominal and Rectovaginal Fistulas

Many fistulas are asymptomatic and require no specific therapy. For symptomatic fistulas, medical therapy is effective in a subset of patients and is usually tried first in outpatients who otherwise are stable. Anti-TNF agents may promote closure in up to 60% within 10 weeks; however, relapse occurs in over one-half of patients within 1 year despite continued therapy. Surgical therapy is required for symptomatic fistulas that do not respond to medical therapy. Fistulas that arise above (proximal to) areas of intestinal stricturing commonly require surgical treatment.

D. Perianal Disease

Patients with fissures, fistulas, and skin tags commonly have perianal discomfort. Successful treatment of active intestinal disease also may improve perianal disease. Specific treatment of perianal disease can be difficult and is best approached jointly with a surgeon with an expertise in colorectal disorders. Pelvic MRI is the best noninvasive study for evaluating perianal fistulas. Patients should be instructed on proper perianal skin care, including gentle wiping with a premoistened pad (baby wipes) followed by drying with a cool hair dryer, daily cleansing with sitz baths or a water wash, and use of perianal cotton balls or pads to absorb drainage. Oral antibiotics (metronidazole, 250 mg three times daily, or ciprofloxacin, 500 mg twice daily) may promote symptom improvement or healing in patients with fissures or uncomplicated fistulas; however, recurrent symptoms are common. Immunomodulators or anti-TNF agents or both promote short-term symptomatic improvement from anal fistulas in two-thirds of patients and complete closure in up to one-half of patients; however, less than one-third maintain symptomatic remission during long-term maintenance treatment.

Anorectal abscesses should be suspected in patients with severe, constant perianal pain, or perianal pain in association with fever. Superficial abscesses are evident on perianal examination, but deep perirectal abscesses may require digital examination or pelvic CT or MR scan. Depending on the abscess location, surgical drainage may be achieved by incision, or catheter or seton placement. Surgery should be considered for patients with severe, refractory symptoms but is best approached after medical therapy of the Crohn disease has been optimized.

E. Carcinoma

Patients with colonic Crohn disease are at increased risk for developing colon carcinoma; hence, annual screening colonoscopy to detect dysplasia or cancer is recommended for patients with a history of 8 or more years of Crohn colitis. Patients with Crohn disease also have an increased risk of lymphoma and small bowel adenocarcinoma; however, both are rare.

F. Hemorrhage

Unlike ulcerative colitis, severe hemorrhage is unusual in Crohn disease.

G. Malabsorption

Malabsorption may arise after extensive surgical resections of the small intestine and from bacterial overgrowth in patients with enterocolonic fistulas, strictures, and stasis. Serum levels of vitamins A, D, and B_{12} should be obtained at diagnosis and monitored periodically in patients with ileal inflammation or resection.

Differential Diagnosis

Chronic cramping abdominal pain and diarrhea are typical of both IBS and Crohn disease, but radiographic examinations are normal in the former. Celiac disease may cause diarrhea with malabsorption. Acute fever and right lower quadrant pain may resemble appendicitis or *Yersinia enterocolitica* enteritis. Intestinal lymphoma causes fever,

pain, weight loss, and abnormal small bowel radiographs that may mimic Crohn disease. Patients with undiagnosed AIDS may present with fever and diarrhea. Segmental colitis may be caused by tuberculosis, *E histolytica, Chlamydia*, or ischemic colitis. *C difficile* or CMV infection may develop in patients with inflammatory bowel disease, mimicking disease recurrence. In patients from tuberculosis-endemic countries, it can be extremely difficult to distinguish active intestinal tuberculosis from Crohn disease, even with biopsies and PCR analyses. Diverticulitis or appendicitis with abscess formation may be difficult to distinguish acutely from Crohn disease. NSAIDs may exacerbate inflammatory bowel disease and may also cause NSAID-induced colitis characterized by small bowel or colonic ulcers, erosions, or strictures, often most severe in the terminal ileum and right colon.

Treatment of Active Disease

Crohn disease is a chronic lifelong illness characterized by exacerbations and remissions. Although no specific therapy exists, early treatment that successfully achieves endoscopic and histologic remission is associated with a reduced risk of disease complications, including fistulas, abscesses, and surgeries. Risk stratification is therefore appropriate to guide selection of the optimal treatment. Risk factors for an aggressive disease course include (1) young age at disease onset; (2) early need for corticosteroids; (3) perianal disease, fistulizing or stricturing disease, or upper GI involvement; (4) laboratory markers of severe inflammation, including low albumin or hemoglobin, elevated CRP, or elevated fecal calprotectin; or (5) endoscopic findings of deep ulcerations. Approximately, 20–30% of patients have mild, intermittent disease with a nonprogressive course. Most patients have moderate to severe disease for which early use of biologic therapies is warranted to control inflammation and to slow or arrest disease progression.

A. Mild/Low-Risk Disease

Patients may be characterized as having mild disease with a low risk of disease progression if they have mild symptoms, no significant weight loss, normal or only mildly elevated inflammatory markers (CRP, fecal calprotectin, serum albumin), absence of intestinal complications (stricturing, abscess, fistula, perianal disease), and limited intestinal involvement with superficial mucosal ulcers.

1. Nutrition—Patients should eat a well-balanced diet with as few restrictions as possible. Eating smaller but more frequent meals may be helpful. Patients with diarrhea should be encouraged to drink fluids to avoid dehydration. Many patients report that certain foods worsen symptoms, especially fried or greasy foods. Because lactose intolerance is common, a trial off dairy products is warranted if flatulence or diarrhea is a prominent complaint. Probiotics have not proven beneficial for Crohn disease.

2. Symptomatic therapy—Loperamide (2–4 mg) may be given for diarrhea as needed up to four times daily.

3. Drug therapy—It is recommended that therapy for mild, low-risk Crohn disease begin with medications that are less potent but have a lower risk of adverse effects. Recommended drug treatment depends on the location of disease involvement.

A. Terminal ileum or ascending colon disease—For patients with mild disease involving the terminal ileum or ascending colon, initial treatment is recommended with extended-release budesonide (Entocort), 9 mg once daily for 8 weeks, which induces remission in 50–70% of patients. If disease remission is achieved, budesonide is tapered over 2–4 weeks in 3 mg increments and the patient observed. For treatment of mild ileocolonic Crohn disease, 5-ASA agents remain in widespread clinical use despite an absence of clinical trial data supporting their efficacy. Formulations that release mesalamine in the distal small intestine (Asacol 2.4–4.8 g/day or Pentasa 2–4 g/day) are most often prescribed.

B. Left-sided or diffuse colitis—For patients with mild colitis that is diffuse or involves only the left side of the colon, oral corticosteroids (prednisone or prednisolone) are recommended. The initial dose of either agent is 40 mg once daily for 1–2 weeks, followed in those who respond by gradual tapering of 5–10 mg/week over 4–8 weeks. Sulfasalazine (1.5–3 g orally twice daily) appears effective in improving symptoms and inducing remission in patients with mild Crohn disease involving the colon (not small intestine) and is recommended in current treatment guidelines. Sulfasalazine is associated with potentially severe side effects in up to 30% of patients (see Inflammatory Bowel Disease: Pharmacologic Therapy). For patients who respond, sulfasalazine 2–4 g/day may be continued as long-term maintenance. Because of sulfasalazine's side effects, many clinicians prescribe other oral 5-ASA agents for mild Crohn colitis despite an absence of clinical data supporting efficacy. Such agents include those that release 5-ASA throughout the colon: delayed-release mesalamine (Lialda or Asacol 2.4–4.8 g/day; Apriso 2.25–4.5 g/day) and balasalazide 2.25 g three times daily.

C. Long-term follow-up—In patients with mild Crohn disease who respond to initial therapy with budesonide or prednisone, treatment should be discontinued and the patient monitored periodically for disease recurrence (symptoms, CRP, fecal calprotectin, or endoscopy every 1–2 years). Patients who respond to treatment with sulfasalazine or other 5-ASA formulations should continue long-term maintenance therapy. Patients with mild disease who either do not respond to initial therapy or those who experience symptom relapse more than once every 1–2 years following tapering of corticosteroids should be reclassified as moderate to high risk for disease progression and "stepped up" to more potent therapies (oral corticosteroids, immunomodulators, or biologic agents).

B. Moderate to Severe/High-Risk Crohn Disease

Moderate to severe disease may be characterized by frequent diarrhea, weight loss, daily abdominal pain, abdominal tenderness, and perianal disease. Evidence of significant inflammation includes elevated CRP (greater than 5 mg/dL); anemia; low serum albumin; elevated fecal calprotectin

(greater than 150–200 mcg/g); or the findings of deep ulceration, stricture, or penetrating disease on endoscopy or radiologic imaging. Patients characterized as having moderate to severe Crohn disease warrant early treatment with biologic agents (with or without immunomodulators) to promote sustained clinical remission and intestinal mucosal healing ("endoscopic remission"). The choice of therapies depends on patient age and comorbidities, patient preference, the presence of extraintestinal manifestations, and "tiering" of agents by third-party payors. Sustained clinical remission with intestinal mucosal healing should be the therapeutic goal in most patients; however, this cannot always be achieved.

1. Nutrition—Patients with obstructive symptoms should be placed on a low-roughage diet, ie, no raw fruits or vegetables, popcorn, nuts, etc. TPN sometimes is used short term in patients with active disease and progressive weight loss, especially those awaiting surgery who have malnutrition but cannot tolerate enteral feedings because of high-grade obstruction, high-output fistulas, severe diarrhea, or abdominal pain. Parenteral vitamin B_{12} (1000 mcg subcutaneously per month) and oral vitamin D supplementation commonly are needed for patients with previous ileal resection or extensive terminal ileal disease.

2. Symptomatic therapy—Involvement of the terminal ileum with Crohn disease or prior ileal resection may lead to reduced absorption of bile acids that may induce secretory diarrhea from the colon. Secretory diarrhea responds to agents that bind the malabsorbed bile salts: cholestyramine 2–4 g or colestipol 1–2 g one to three times daily with meals; or colesevelam, 625 mg, one to three tablets twice daily. Patients with extensive ileal disease (requiring more than 100 cm of ileal resection) have severe bile salt malabsorption causing steatorrhea. Such patients may benefit from a low-fat diet; bile salt–binding agents exacerbate the diarrhea and should not be given. Patients with Crohn disease are at risk for the development of small intestinal bacterial overgrowth due to enteral fistulas, ileal resection, and impaired motility and may benefit from a course of broad-spectrum antibiotics (see Bacterial Overgrowth, above). Other causes of diarrhea include lactase deficiency and short bowel syndrome. Use of oral antidiarrheal agents may provide benefit in some patients.

3. Drug therapy—The goal of drug treatment for moderate to severe, high-risk Crohn disease is to induce and maintain clinical disease remission, including mucosal healing, whenever possible.

A. Corticosteroids—Corticosteroids dramatically suppress the acute clinical symptoms and signs in most patients with both small and large bowel disease; however, they do not alter the natural history of the underlying disease. Because of their rapidity of onset, corticosteroids commonly are used in patients with moderate to severe disease to promote early symptomatic improvement while other disease-modifying agents with slower onset of action are initiated. Hospitalization is warranted in some patients with symptoms or signs of severe disease, especially those with high fever, persistent vomiting, evidence of intestinal obstruction, severe weight loss, severe abdominal tenderness, or suspicion of an abscess. In patients with a tender, palpable inflammatory abdominal mass, CT of the abdomen should be obtained prior to administering corticosteroids to rule out an abscess. If no abscess is identified, parenteral corticosteroids (methylprednisolone 40–60 mg daily) should be administered. Outpatients with moderate to severe disease may be treated with oral prednisone or methylprednisolone, 40 mg/day for 1–2 weeks followed by slow tapering of 5–10 mg/week over 4–8 weeks. Remission or significant improvement occurs in greater than 80% of patients after 8–16 weeks of therapy. It is recommended in most patients that a biologic agent be initiated as the corticosteroid is tapered and withdrawn. Use of long-term low corticosteroid doses should be avoided because of associated complications. If a decision is made not to initiate a biologic agent, long-term treatment with an immunomodulator (azathioprine, mercaptopurine, or methotrexate) is recommended to attempt to provide a steroid-free disease maintenance. However, approximately 20% of patients cannot be completely withdrawn from corticosteroids without experiencing a symptomatic flare-up.

B. Biologic therapies—Induction therapy with a biologic agent is recommended for almost all patients with moderate to severe Crohn disease; those with a favorable clinical response to induction treatment should be maintained on long-term therapy with a goal of achieving clinical and endoscopic remission. Current treatment options include anti-TNF monoclonal antibodies (infliximab, adalimumab, certolizumab), anti-integrin monoclonal antibody (vedolizumab), and anti-IL-12/23 monoclonal antibody (ustekinumab) (see Inflammatory Bowel Disease: Pharmacology, above). In the absence of head-to-head comparative trials of these agents, relative differences in efficacy and safety are suggested by network meta-analyses. The choice of biologic agent depends on the disease severity, patient age and comorbidities, patient preference, and drug cost/pharmacy tiering.

*(1) Anti-TNF therapies—*For most patients with moderate to severe Crohn disease, two anti-TNF therapies (infliximab or adalimumab) are recommended as the preferred first-line agents to induce remission either as monotherapy or in combination with immunomodulating agents (azathioprine, mercaptopurine, or methotrexate). Up to two-thirds of patients have significant clinical improvement during acute induction therapy (see Inflammatory Bowel Disease: Pharmacology above for dosing). Although direct comparisons of these anti-TNF agents are unavailable, indirect evidence suggests that intravenous, weight-based infliximab infusion may be preferred to subcutaneous, fixed-dose adalimumab for patients with severe disease, extraintestinal manifestations, perianal disease, or obesity. Certolizumab appears inferior to other anti-TNF agents. Compared with anti-TNF monotherapy, clinical trials suggest that combination of an anti-TNF agent (infliximab or adalimumab) with an immunomodulator (azathioprine, mercaptopurine, or methotrexate) achieves higher rates of clinical and mucosal healing. This benefit is ascribed to increased anti-TNF serum drug levels, reduced development of neutralizing anti-TNF antibodies, and synergistic

anti-inflammatory effects. Despite these benefits, the role of combination therapy versus monotherapy is controversial due to an increased risk of adverse events, including myelosuppression, infections, and malignancies (lymphoma, skin cancer). Due to the complexity and higher risks of combination therapy, many clinicians prefer monotherapy with drug monitoring to optimize anti-TNF trough levels and reduce the risk of developing anti-drug antibodies. Retrospective clinical trial data suggest that remission rates are similar between combination therapy and anti-TNF monotherapy when adjusted for trough levels. Combination therapy is favored for patients at higher risk for disease progression or who previously developed antibodies to a biologic agent.

After initial clinical response, symptom relapse occurs in more than 80% of patients within 1 year in the absence of further maintenance therapy. Therefore, scheduled maintenance therapy is usually recommended (eg, infliximab, 5 mg/kg infusion every 8 weeks; or adalimumab, 40 mg subcutaneous injection every 1–2 weeks). With long-term maintenance therapy, approximately two-thirds of patients have continued clinical response and up to one-half have complete symptom remission. Serum anti-TNF trough levels and drug antibody levels may guide therapy in patients who have lost response. Patients with low serum anti-TNF trough levels and absent drug antibodies should receive increased anti-TNF dosing (infliximab 10 mg/kg; adalimumab 80 mg) or decreased dosing intervals (infliximab every 6 weeks; adalimumab every week). Patients with high antibodies to the anti-TNF agent and low anti-TNF trough levels should be switched to another anti-TNF agent. Patients with inadequate response despite adequate anti-TNF trough levels should be changed to an alternative biologic agent, such as vedolizumab or ustekinumab. In patients receiving combination therapy, consideration should be given to stopping or reducing the dose of the immunomodulating agent after 6–12 months for patients in remission, most especially men younger than age 30 years who have a higher risk of hepatosplenic T-cell lymphoma and for adults older than age 50–60 years in whom there is a higher risk of lymphoma and of infectious complications.

(2) Anti-IL-12/IL-23 antibody—Ustekinumab is also appropriate as first-line induction therapy for patients with moderate to severe Crohn disease and is preferred in those deemed to be at increased risk for complications of anti-TNF therapy. It is also recommended in patients who did not respond to or lost response to prior anti-TNF therapy. In a phase 3 trial involving 741 patients with Crohn disease in whom anti-TNF therapy failed, clinical response was seen in 34% of patients 6 weeks after a single dose of intravenous ustekinumab compared to 21.5% with placebo. In a second phase 3 trial composed of patients in whom conventional therapy with immunomodulators or corticosteroids (but not anti-TNF) had failed, clinical improvement occurred in 55% compared to 28.7% with placebo. Among patients from both induction trials who were enrolled in a chronic maintenance trial (ustekinumab versus placebo subcutaneously every 8 weeks), 53% of those given ustekinumab were in clinical remission at week 44 versus 36% given the placebo.

(3) Anti-integrins—Vedolizumab may be chosen as a first-line agent for induction therapy in patients with moderate Crohn disease who are deemed at increased risk for complications from anti-TNF therapy due to advanced age, multiple comorbidities, or prior malignancy. Vedolizumab may also be used as a second- or third-line agent in patients who have not responded or lost response to anti-TNF agents or ustekinumab. For both first-line therapy in patients not previously treated with biologic agents and second-line therapy in patients who did not respond to anti-TNF therapy, a 2021 AGA guideline provides a "conditional" recommendation for vedolizumab versus a "strong" recommendation for ustekinumab due to low certainty of evidence. In a phase 3 trial, among patients demonstrating initial clinical improvement with vedolizumab induction therapy, 39% of patients treated with long-term vedolizumab (300 mg intravenously every 8 weeks) were in remission at 1 year compared with 21.6% of patients given placebo. Vedolizumab may be less effective than anti-TNF or ustekinumab in the treatment of extraintestinal manifestations and fistulous disease.

Indications for Surgery

Over 50% of patients will require at least one surgical procedure. The main indications for surgery are intractability to medical therapy, intra-abdominal abscess, massive bleeding, symptomatic refractory internal or perianal fistulas, and intestinal obstruction. Patients with chronic obstructive symptoms due to a short segment of ileal stenosis are best treated with resection or stricturoplasty (rather than long-term medical therapy), which promotes rapid return of well-being and elimination of corticosteroids. After surgery, endoscopic evidence of recurrence occurs in 60% within 1 year. Endoscopic recurrence precedes clinical recurrence by months to years; clinical recurrence occurs in 20% of patients within 1 year and 80% within 10–15 years. In a controlled trial of 297 patients undergoing ileocolonic resection, endoscopic recurrence occurred in 30% of patients treated with infliximab every 8 weeks compared with 60% treated with placebo. It may be reasonable to initiate empiric infliximab postoperatively for patients at high risk for disease recurrence and to perform endoscopy in low-risk patients 6 months after surgery in order to identify patients with early endoscopic recurrence who may benefit from biologic therapy.

Prognosis

With proper medical and surgical treatment, the majority of patients are able to cope with this chronic disease and its complications and lead productive lives. Few patients die as a direct consequence of the disease.

When to Refer

- For expertise in endoscopic procedures or capsule endoscopy.
- For follow-up of any patient requiring hospitalization.
- Patients with moderate to severe disease for whom therapy with immunomodulators or biologic agents is being considered.
- When surgery may be necessary.

When to Admit

- An intestinal obstruction is suspected.
- An intra-abdominal or perirectal abscess is suspected.
- A serious infectious complication is suspected, especially in patients who are immunocompromised due to concomitant use of corticosteroids, immunomodulators, or anti-TNF agents.
- Patients with severe symptoms of diarrhea, dehydration, weight loss, or abdominal pain.
- Patients with severe or persisting symptoms despite treatment with corticosteroids.

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2. Ulcerative Colitis

ESSENTIALS OF DIAGNOSIS

- Bloody diarrhea.
- Lower abdominal cramps and fecal urgency.
- Anemia, low serum albumin.
- Negative stool studies for pathogens.
- Sigmoidoscopy is the key to diagnosis.

General Considerations

Ulcerative colitis is a chronic, recurrent disease involving only the colon. It is characterized by diffuse mucosal inflammation that results in friability, erosions, and ulcers with bleeding. Ulcerative colitis invariably involves the rectum and may extend proximally in a continuous fashion to involve part or all of the colon. Approximately one-fourth of patients have disease confined to the rectosigmoid region (proctosigmoiditis); one-half have disease that extends to the splenic flexure (left-sided colitis); and one-fourth have disease that extends more proximally (extensive colitis). In patients with distal colitis, the disease progresses with time to more extensive involvement in 25%. There is some correlation between disease extent and symptom severity. In most patients, the disease is characterized by periods of symptomatic flare-ups and periods of mild activity or remission. Approximately 15% of patients may have an aggressive course with increased risk of hospitalization or surgery. Of patients hospitalized with severe colitis, colectomy is required in up to 30% for unresponsive or "fulminant" disease. Ulcerative colitis is more common in nonsmokers and former smokers. Disease severity may be lower in active smokers and may worsen in patients who stop smoking. Appendectomy before the age of 20 years for acute appendicitis is associated with a reduced risk of developing ulcerative colitis.

Clinical Findings

A. Symptoms and Signs

The clinical profile in ulcerative colitis is highly variable. Bloody diarrhea is the hallmark. Several clinical and laboratory parameters help classify patients as having mild, moderate, or severe disease (Table 15–12). Patients should be asked about stool frequency, the presence and amount of rectal bleeding, cramps, abdominal pain, fecal urgency, tenesmus, and extraintestinal symptoms. Physical examination should focus on the patient's volume status as determined by orthostatic blood pressure and pulse measurements and by nutritional status. On abdominal examination, the clinician should look for tenderness and evidence of peritoneal inflammation. Red blood may be present on digital rectal examination.

1. Mild to moderate disease—Patients with mild to moderate disease have fewer than four to six bowel movements per day, mild to moderate rectal bleeding, and no constitutional symptoms. Stools may be formed or loose in consistency. Because of rectal inflammation, there is fecal urgency and tenesmus. Left lower quadrant cramps relieved by defecation are common, but there is no significant abdominal pain or tenderness. There may be mild anemia and hypoalbuminemia.

2. Severe disease—Patients with severe disease have more than six bloody bowel movements per day, resulting in

Table 15–12. Ulcerative colitis: assessment of disease activity.

	Mild	Moderate	Severe
Stool frequency (per day)	< 4	4–6	> 6–10
Blood in stools	Intermittent	Frequent	Continuous
Hematocrit (%)	Normal	30–40	< 30
CRP	Normal or elevated	Elevated	Elevated
ESR (mm/h)	< 30	> 30	> 30
Endoscopy Mayo Subscore	1	2–3	3

severe anemia, hypovolemia, and impaired nutrition with hypoalbuminemia. Abdominal pain and tenderness are present. "Fulminant colitis" is a subset of severe disease characterized by rapidly worsening symptoms with signs of toxicity.

B. Laboratory Findings

The degree of abnormality of the hematocrit, serum albumin, and inflammatory markers (ESR and CRP) reflects disease severity (Table 15–12).

C. Endoscopy

In acute colitis, the diagnosis is readily established by sigmoidoscopy. The mucosal appearance is characterized by edema, friability, mucopus, and erosions. The "Mayo" endoscopic scoring system is commonly used in clinical practice and therapeutic trials. A score of 0 indicates normal or inactive colitis; 1 indicates erythema, decreased vascularity; 2 indicates friability, marked erythema, erosions; and 3 indicates ulcerations, severe friability, spontaneous bleeding. Mayo endoscopic scores 1–2 are consistent with mild to moderate disease clinical activity, and Mayo scores 2–3 are usually seen in patients with moderate to severe clinical activity. Colonoscopy should not be performed in patients with fulminant disease because of the risk of perforation. After patients have demonstrated improvement on therapy, colonoscopy is performed to determine the extent of disease.

D. Imaging

Abdominal imaging with plain radiographs or CT is obtained in patients with severe colitis to look for significant colonic dilation. Barium enemas are of little utility and may precipitate toxic megacolon.

Differential Diagnosis

The initial presentation of ulcerative colitis is indistinguishable from other causes of colitis, clinically as well as endoscopically. Thus, the diagnosis of idiopathic ulcerative colitis is reached after excluding other known causes of colitis. Infectious colitis should be excluded by sending stool specimens for routine testing to exclude *Salmonella, Shigella*, *Campylobacter*, *E coli* O157, *C difficile*, and amebiasis. Where available, microbial assessment using multiplex molecular techniques provides results within 1–4 hours with excellent sensitivity and is preferred to conventional labor-intensive stool microscopy, culture, and toxin testing. CMV colitis occurs in immunocompromised patients, including patients receiving prolonged corticosteroid therapy, and is diagnosed on mucosal biopsy. Gonorrhea, chlamydial infection, herpes, and syphilis are considerations in sexually active patients with proctitis. In older adult patients with CVD, ischemic colitis may involve the rectosigmoid. A history of radiation to the pelvic region can result in proctitis months to years later. Crohn disease involving the colon but not the small intestine may be confused with ulcerative colitis. In 10% of patients, a distinction between Crohn disease and ulcerative colitis may not be possible.

Treatment

There are three main treatment objectives: (1) to terminate the acute, symptomatic attack; (2) to achieve complete remission of clinical and endoscopic disease activity; and (3) to prevent recurrence of attacks. The treatment of acute ulcerative colitis depends on the extent of colonic involvement and the severity of illness. Patients with systemic signs of inflammation (ie, anemia, low serum albumin, elevated CRP or ESR levels) and ulcerations with extensive disease on colonoscopy are at increased risk for hospitalization or surgery, and early aggressive therapy with biologic agents is warranted.

A. Mild to Moderate Distal Colitis

Patients with disease confined to the rectum or rectosigmoid region generally have mild to moderate but distressing symptoms. Patients may be treated with topical mesalamine, topical corticosteroids, or oral aminosalicylates (5-ASA) according to patient preference and cost considerations. Topical mesalamine is the drug of choice and is superior to topical corticosteroids and oral 5-ASA. Mesalamine is administered as a suppository, 1000 mg once daily at bedtime for proctitis, and as an enema, 4 g at bedtime for proctosigmoiditis, for 4–8 weeks, with 75% of patients improving. Patients who either decline or are unable to manage topical therapy may be treated with oral 5-ASA, as discussed below. Although topical corticosteroids are a less expensive alternative to mesalamine, they are also less effective. Hydrocortisone enema or foam (80–100 mg) or budesonide foam are prescribed for proctitis or proctosigmoiditis. Systemic effects from short-term use are very slight. For patients with distal disease who do not improve with topical or oral mesalamine therapy within 6 weeks, the following options may be considered: (1) a combination of a topical agent with an oral 5-ASA agent; (2) topical corticosteroid; or (3) addition of oral prednisone (as described below) or budesonide MMX 9 mg/day for 4–8 weeks to rectal and oral 5-ASA.

Most patients with proctitis or proctosigmoiditis who achieve complete remission with oral or rectal 5-ASA should continue indefinitely on the same therapy to reduce the likelihood of symptomatic relapse. Maintenance treatment with 5-ASA reduces the 12-month relapse rate from 75% to less than 40%. Some patients, however, may prefer intermittent therapy for symptomatic relapse. Topical corticosteroids are ineffective for maintaining remission of distal colitis.

B. Mild to Moderate Colitis

1. 5-ASA agents—Disease extending above the sigmoid colon is best treated with both an oral and rectal 5-ASA agent. For induction of remission, the optimal dose of oral 5-ASA (mesalamine) is 2–3 g once daily in combination with mesalamine 1 g suppository or 4 g enema at bedtime. Most patients improve within 4–8 weeks. Some patients may prefer to initiate therapy with an oral agent, adding topical therapy if initial response is inadequate. These agents achieve clinical improvement in 75% of patients and

remission in 20–30%. Oral sulfasalazine (1.5–2 g twice daily) is uncommonly used due to its side effects.

2. Corticosteroids—Patients with mild to moderate colitis who do not improve within 4–8 weeks of 5-ASA therapy should have an oral corticosteroid therapy added with budesonide MMX or prednisone. Budesonide MMX (Uceris) 9 mg/day orally for 4–8 weeks may be preferred in mild to moderate colitis due to its low incidence of corticosteroid-associated side effects, especially in those for whom other systemic corticosteroids are deemed high risk. For patients who require more than one course of corticosteroid therapy every 1–2 years for symptomatic relapse, treatment should be "stepped up" to include a thiopurine (azathioprine or mercaptopurine) or a biologic agent, as described below for Moderate to Severe Colitis.

C. Moderate to Severe Colitis

1. Corticosteroids—An oral corticosteroid (prednisone or methylprednisolone) is commonly prescribed as the first-line agent for nonhospitalized patients with moderate to severe colitis or as second-line therapy in patients in whom initial 5-ASA therapy was ineffective. The initial oral dose of prednisone is 40 mg daily. Rapid improvement is observed in most cases within 2 weeks. Thereafter, tapering of prednisone should proceed by 5–10 mg/wk. After tapering to 20 mg/day, slower tapering (2.5 mg/wk) is sometimes required. Complete tapering of prednisone without symptomatic flare-ups is possible in the majority of patients. Corticosteroids should not be continued long-term to control symptoms because of an unacceptable risk of adverse side effects. Patients achieving remission should be maintained on oral mesalamine (2–4 g/day). Up to 30% of patients either do not respond to prednisone or have symptomatic flares during tapering that prevent its complete withdrawal. The addition of a thiopurine (azathioprine or mercaptopurine) is sometimes used to promote complete steroid withdrawal and maintain long-term remission. Biologic agents or small molecules (tofacitinib, ozanimod) are recommended for patients in whom corticosteroids cannot be completely withdrawn or who require more than one course of corticosteroids every 1–2 years.

2. Biologic agents and small molecules—Anti-TNF antibodies (infliximab, adalimumab, golimumab), vedolizumab (integrin antibody), ustekinumab (IL-12/23 antibody), tofacitinib (Janus kinase inhibitor), and ozanimod (sphingosine 1-phoshate receptor modulator) have demonstrated efficacy for treatment of moderate to severe colitis. The preferred agent depends on several considerations: prior exposure and response to biologic agents; disease severity; patient comorbidities; preferred mode of administration (intravenous, subcutaneous, oral); and pharmacy/insurance company tiering.

a. Treatment of patients naïve to prior biologic therapy—A 2020 AGA guideline recommends either infliximab or vedolizumab as first-line therapies for moderate to severe colitis based on their efficacy and safety profiles. These two agents had the highest rankings of all biologic agents for induction of clinical remission in a 2020 network meta-analysis. Although infliximab may be the more effective agent (especially for severe disease), vedolizumab may be the preferred first-line therapy in older adult patient who have increased medical comorbidities due to its significantly lower incidence of infectious complications.

An induction regimen of infliximab (5 mg/kg intravenously administered at 0, 2, and 6 weeks) results in clinical response in 65% of patients. During long-term maintenance treatment with infliximab (5–10 mg/kg every 4–8 weeks), clinical improvement or remission is achieved in approximately 50% of patients. Network meta-analyses suggest superiority of infliximab (weight-based, intravenous infusion) over the other anti-TNF agents adalimumab and golimumab (fixed-dose, subcutaneous injection). Treatment with adalimumab or golimumab may nonetheless be selected in patients with moderate (not severe) disease who prefer the convenience of subcutaneous, self-injection.

Vedolizumab induction (300 mg intravenously at 0, 2, and 6 weeks) led to clinical improvement in 47.1% of patients compared with 25.5% who were given placebo. Among patients who demonstrated initial clinical improvement, 41.8% of those given long-term maintenance treatment with vedolizumab (300 mg intravenously every 8 weeks) were in clinical remission at 1 year compared with 15.9% of those given placebo. The 2019 VARSITY trial randomized patients with moderate to severe ulcerative colitis to induction and maintenance therapy with vedolizumab versus adalimumab. At 1 year, clinical remission (31.3% vs 22.5%) and endoscopic improvement (39.7% vs 27.7%) were seen in significantly more patients treated with vedolizumab than adalimumab. This was the first controlled trial in ulcerative colitis comparing agents from different biologic classes. Due to its efficacy and superior safety profile, vedolizumab may become the preferred first-line biologic agent for the treatment of moderate ulcerative colitis.

When initiating induction therapy with anti-TNF agents, many clinicians add an immunomodulator (azathioprine, mercaptopurine, or methotrexate) for the first year to increase the likelihood of disease remission and to reduce the development of antibodies that may result in secondary loss of response to anti-TNF therapies. If monotherapy is preferred, proactive drug monitoring of serum trough levels and anti-drug antibody titers should be obtained during induction and maintenance therapy in order to optimize drug dosing. Vedolizumab and ustekinumab have a lower incidence of anti-drug antibodies; hence, immunomodulator cotherapy is not generally prescribed.

Ozanimod is a once daily oral small molecule that was approved by the FDA in 2021 for the treatment of moderate to severe ulcerative colitis. During the first week of therapy, ozanimod dosage is titrated upward (days 1–4: 0.23 mg orally once daily; days 5–7: 0.46 mg orally once daily). On day 8 and thereafter, the dosage is 0.92 mg orally once daily. In phase 3 trials of patients with moderate to severe ulcerative colitis who had not previously received biologic therapy, ozanimod treatment resulted in higher clinical response than placebo after 10 weeks (52.5% versus 29.1%) and higher clinical remission after 52 weeks (41% versus 22%). Among patients who had previously not

responded to treatment with an anti-TNF agent, ozanimod treatment achieved clinical response after 10 weeks in 36.9% versus 18.5% with placebo. Clinical experience with this novel agent is limited, but it should be considered in non-hospitalized, biologically naive patients who prefer the convenience of oral therapy.

b. Second-line treatment for patients who have not responded to infliximab—In patients with moderate to severe colitis who have not responded to or lost response to infliximab, the 2020 AGA treatment guideline recommends ustekinumab or tofacitinib rather than vedolizumab or adalimumab as second-line therapy based on network meta-analyses. In phase 3 trials, the clinical response rates at 8 weeks following intravenous administration of ustekinumab 6 mg/kg vs placebo were 62% vs 31%, respectively. Among responders who entered long-term maintenance treatment with ustekinumab 90 mg or placebo subcutaneous injection every 8 weeks, clinical remission was significantly higher with ustekinumab (44%) than with placebo (24%).

Tofacitinib, an oral, small-molecule JAK 1/3 inhibitor, was approved by the FDA in 2018 for the treatment of moderate to severe ulcerative colitis. However, in 2019 the FDA issued a black box warning about an increased risk of thrombosis and death in rheumatoid arthritis patients treated with tofacitinib 10 mg orally twice daily for prolonged periods. Therefore, the 2020 AGA treatment guideline recommends that tofacitinib currently be restricted to second-line therapy in patients who have not responded or who have lost response to anti-TNF therapy. A network meta-analysis of controlled trials found that tofacitinib ranked highest among therapies for induction of remission in patients who have received anti-TNF therapy.

3. Probiotics—Probiotics have not demonstrated significant benefit versus placebo in the treatment of mild to moderate ulcerative colitis in randomized, controlled trials.

D. Severe and Fulminant Colitis

About 15% of patients with ulcerative colitis have a more severe course. Of these, a small subset has a fulminant course with rapid progression of symptoms over 1–2 weeks and signs of severe toxicity. These patients appear quite ill, with fever, prominent hypovolemia, hemorrhage requiring transfusion, and abdominal distention with tenderness. Toxic megacolon develops in less than 2% of cases of ulcerative colitis. It is characterized by colonic dilation of more than 6 cm on plain films with signs of toxicity.

1. General measures—Discontinue all oral intake for 24–48 hours or until the patient demonstrates clinical improvement. TPN is indicated only in patients with poor nutritional status or if feedings cannot be reinstituted within 7–10 days. All opioid or anticholinergic agents should be discontinued. Restore circulating volume with fluids, correct electrolyte abnormalities, and consider transfusion for significant anemia (hematocrit less than 25–28%). A plain abdominal radiograph or CT scan should be ordered on admission to look for evidence of colonic dilation. Send stools for assessment of bacterial pathogens, *C difficile* and parasites, either by conventional bacterial culture, *C difficile* toxin assay, and ova and parasite examinations or by rapid, multiplex PCR assay. CMV superinfection should be considered in patients receiving long-term immunosuppressive therapy who are unresponsive to corticosteroid therapy. Due to a high risk of venous thromboembolic (VTE) disease, VTE prophylaxis should be administered to all hospitalized patients with inflammatory bowel disease. Surgical consultation should be sought for all patients with severe disease.

Patients with fulminant disease are at higher risk for toxic megacolon or perforation and must be monitored closely. Abdominal examinations should be repeated to look for evidence of worsening distention or pain. A 2020 AGA guideline does not recommend the use of empiric broad-spectrum antibiotics in the absence of confirmed infection. In addition to the therapies outlined above, nasogastric suction should be initiated. Patients with toxic megacolon should be instructed to roll from side to side and onto the abdomen in an effort to decompress the distended colon. Serial abdominal plain films should be obtained to look for worsening dilation or signs of ischemia. Patients with fulminant disease or toxic megacolon who worsen or do not improve within 48–72 hours should undergo surgery to prevent perforation. If the operation is performed before perforation, the mortality rate should be low.

2. Corticosteroid therapy—Methylprednisolone, 40–60 mg, is administered intravenously. There appears to be no difference in efficacy between single-dose, divided dose, or continuous infusion regimens. Higher or "pulse" doses are of no benefit. Hydrocortisone enemas (100 mg) may also be administered twice daily for treatment of urgency or tenesmus. Clinical improvement with systemic corticosteroids should be evident within 3–5 days in 50–75% of patients. Once symptomatic improvement has occurred, oral fluids are reinstituted. If these fluids are well tolerated, intravenous corticosteroids are discontinued and the patient is started on oral prednisone (as described for moderate disease). Patients without significant improvement within 3–5 days of intravenous corticosteroid therapy should be referred for surgery or considered for anti-TNF therapies or cyclosporine.

3. Anti-TNF therapies—Intravenous infusion of infliximab, 5–10 mg/kg, has been shown in uncontrolled and controlled studies to be effective in treating severe colitis in patients who did not improve within 4–7 days of intravenous corticosteroid therapy. In a controlled study of patients hospitalized for ulcerative colitis, colectomy was required within 3 months in 69% who received placebo therapy, compared with 47% who received infliximab. Thus, infliximab therapy should be considered in patients with severe ulcerative colitis who have not improved with intravenous corticosteroid therapy. Recent studies have demonstrated more rapid clearance of infliximab in patients with severe ulcerative colitis. Uncontrolled trials have found lower colectomy rates in patients administered higher doses of infliximab (three infusions of 5–10 mg/kg within 2–3 weeks) than with conventional dosing (5 mg/kg at 0, 2, and 6 weeks).

4. Cyclosporine—Intravenous cyclosporine (2–4 mg/kg/day as a continuous infusion) benefits 60–75% of patients with severe colitis who have not improved after 7–10 days of corticosteroids, but it is associated with significant toxicity (nephrotoxicity, seizures, infection, hypertension). Up to two-thirds of responders may be maintained in remission with a combination of oral cyclosporine for 3 months and long-term therapy with mercaptopurine or azathioprine. A 2011 randomized study of patients with severe colitis refractory to intravenous corticosteroids found similar response rates (85%) with cyclosporine and infliximab therapy.

5. Surgical therapy—Patients with severe disease who do not improve after corticosteroid, infliximab, or cyclosporine therapy are unlikely to respond to further medical therapy, and surgery is recommended.

Risk of Colon Cancer

In patients with ulcerative colitis with disease proximal to the rectum and in patients with Crohn colitis, there is an increased risk of developing colon carcinoma. Although older meta-analyses from referral centers reported a high risk (8% after 20 years), more recent systematic reviews of population-based studies report a 2.4-fold increased risk (1.4% after a mean of 14 years of follow-up). Colonoscopies are recommended beginning 8 years after disease diagnosis. The use of high-definition colonoscopes with electronic enhancement or spray application of dilute blue dye (chromoendoscopy) enhances the detection of subtle mucosal lesions, thereby significantly increasing the detection of dysplasia compared with standard colonoscopy. At colonoscopy, all polypoid and nonpolypoid lesions should be resected, when possible, and biopsies obtained of endoscopically unresectable lesions. Subsequent surveillance colonoscopies are performed every 1–5 years, depending on ulcerative colitis extent and activity, and presence of colonic scarring, pseudopolyps, or dysplasia.

Surgery in Ulcerative Colitis

Surgery is required in 25% of patients. Severe hemorrhage, perforation, and documented carcinoma are absolute indications for surgery. Surgery is indicated also in patients with fulminant colitis or toxic megacolon that does not improve within 48–72 hours, in patients with invisible flat dysplasia or non-endoscopically resectable dysplastic lesions on surveillance colonoscopy, and in patients with refractory disease requiring long-term corticosteroids to control symptoms.

Although total proctocolectomy (with placement of an ileostomy) provides complete cure of the disease, most patients seek to avoid it out of concern for the impact it may have on their bowel function, their self-image, and their social interactions. After complete colectomy, patients may have a standard ileostomy with an external appliance, a continent ileostomy, or an internal ileal pouch that is anastomosed to the anal canal (ileal pouch–anal anastomosis). The latter maintains intestinal continuity, thereby obviating an ostomy. Under optimal circumstances, patients have five to seven loose bowel movements per day without incontinence. Endoscopic or histologic inflammation in the ileal pouch ("pouchitis") develops in over 40% of patients within 1 year and in up to 80% over the long term, resulting in increased stool frequency, fecal urgency, cramping, and bleeding, but usually resolves with a 2-week course of oral metronidazole (250–500 mg three times daily) or ciprofloxacin (500 mg twice daily). Patients with frequently relapsing pouchitis may need continuous antibiotics. Probiotics do not appear to be of benefit.

Prognosis

Ulcerative colitis is a lifelong disease characterized by exacerbations and remissions. For most patients, the disease is readily controlled by medical therapy without need for surgery. The majority never require hospitalization. A subset of patients with more severe disease will require surgery, which results in complete cure of the disease. Properly managed, most patients with ulcerative colitis lead close to normal productive lives.

When to Refer

- Colonoscopy: for evaluation of activity and extent of active disease and for surveillance for neoplasia in patients with quiescent disease for more than 8 years.
- For follow-up of any patient requiring hospitalization.

When to Admit

- Patients with severe disease manifested by frequent bloody stools, anemia, weight loss, and fever.
- Patients with fulminant disease manifested by rapid progression of symptoms, worsening abdominal pain, distention, high fever, and tachycardia.
- Patients with moderate to severe symptoms that do not respond to oral corticosteroids and require a trial of bowel rest and intravenous corticosteroids.
- Patients in whom surgical colectomy is indicated.

Danese S et al. Positioning therapies in ulcerative colitis. Clin Gastroenterol Hepatol. 2020;18:1280. [PMID: 31982609]
Deepak P et al. Safety of tofacitinib in a real-world cohort of patients with ulcerative colitis. Clin Gastroenterol Hepatol. 2021;19:1592. [PMID: 32629130]
Feuerstein JD et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. Gastroenterology. 2020;158:1450. [PMID: 30576644]
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Rubin DT et al. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol. 2019;114:384. [PMID: 30840605]
Sandborn WJ et al. Ozanimod as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2021;385:1280. [PMID: 34587385]
Singh S et al. First- and second-line pharmacotherapies for patients with moderate to severe active ulcerative colitis: an updated network meta-analysis. Clin Gastroenterol Hepatol. 2020;18:2179. [PMID: 31945470]

3. Microscopic Colitis

Microscopic colitis is an idiopathic condition that is found in up to 15% of patients who have chronic or intermittent watery diarrhea with normal-appearing mucosa at endoscopy. There are two major subtypes—collagenous colitis and lymphocytic colitis. In both, histologic evaluation of mucosal biopsies reveals chronic inflammation (lymphocytes, plasma cells) in the lamina propria and increased intraepithelial lymphocytes. **Collagenous colitis** is further characterized by the presence of a thickened band (greater than 10 mcm) of subepithelial collagen. Both forms occur more commonly in women, especially in the fifth to sixth decades. Symptoms tend to be chronic or recurrent but may remit in most patients after several years. A more severe illness characterized by abdominal pain, fatigue, dehydration, and weight loss may develop in a subset of patients. The cause of **microscopic colitis** usually is unknown. Several medications have been implicated as etiologic agents, including NSAIDs, PPIs, low-dose aspirin, SSRIs, ACE inhibitors, beta-blockers, and menopausal estrogen hormonal therapy. Diarrhea usually abates within 30 days of stopping the offending medication. Celiac disease may be present in 2–9% of patients and should be excluded with serologic testing (IgA anti-tTG). Treatment is largely empiric since there are few well-designed, controlled treatment trials. Antidiarrheal therapy with loperamide is the first-line treatment for mild symptoms, providing symptom improvement in up to 70%. The next option is delayed-release budesonide (Entocort), 9 mg/day for 6–8 weeks. Budesonide induces clinical remission in greater than 80% of patients; however, relapse occurs in most patients after stopping therapy. Remission is maintained in 75% of patients treated long-term with low doses of budesonide. In clinical practice, budesonide is tapered to the lowest effective dose for suppressing symptoms (3 mg every other day to 6 mg daily). For patients who do not respond to budesonide, uncontrolled studies report that treatment with bile-salt binding agents (cholestyramine, colestipol) or 5-ASAs (sulfasalazine, mesalamine) may be effective in some patients. Less than 3% of patients have refractory or severe symptoms, which may be treated with immunosuppressive agents (azathioprine or methotrexate) or anti-TNF agents (infliximab, adalimumab).

Miehlke S et al. European guidelines on microscopic colitis: United European Gastroenterology and European Microscopic Colitis group statement and recommendations. United European Gastroenterol J. 2021;9:13. [PMID: 33619914]
Zylberberg HM et al. Medication use and microscopic colitis: a multicentre retrospective cohort study. Aliment Pharmacol Ther. 2021;54:526. [PMID: 33852749]

DIVERTICULAR DISEASE OF THE COLON

Colonic diverticulosis increases with age, ranging from a prevalence of 5% in those under age 40 to over 50% by age 60 years in Western societies. Most are asymptomatic, discovered incidentally at endoscopy or on barium enema. Complications occur in less than 5%, including GI bleeding and diverticulitis.

Colonic diverticula may vary in size from a few millimeters to several centimeters and in number from one to several dozen. Almost all patients with diverticulosis have involvement in the sigmoid and descending colon; however, only 15% have proximal colonic disease.

For over 40 years, it has been believed that diverticulosis arises after many years of a diet deficient in fiber. Recent epidemiologic studies challenge this theory, finding no association between the prevalence of asymptomatic diverticulosis and low dietary fiber intake or constipation. Thus, the etiology of diverticulosis is uncertain. The extent to which abnormal motility and hereditary factors contribute to diverticular disease is unknown. Patients with abnormal connective tissue are also disposed to development of diverticulosis, including Ehlers-Danlos syndrome, Marfan syndrome, and systemic sclerosis.

1. Uncomplicated Diverticulosis

More than 90% of patients with diverticulosis have uncomplicated disease and no specific symptoms. In most, diverticulosis is an incidental finding detected during colonoscopy. Some patients have nonspecific complaints of chronic constipation, abdominal pain, or fluctuating bowel habits. Physical examination is usually normal but may reveal mild left lower quadrant tenderness with a thickened, palpable sigmoid and descending colon. Screening laboratory studies should be normal in uncomplicated diverticulosis.

There is no reason to perform imaging studies for the purpose of diagnosing asymptomatic, uncomplicated disease. Diverticula are well seen on colonoscopy and CT. Involved segments of colon may also be narrowed and deformed.

Patients in whom diverticulosis is discovered should be encouraged to increase dietary fiber either through diet (fruits, vegetables, whole grains) or fiber supplements (psyllium, methylcellulose), which is associated with a lower risk of diverticulitis in prospective cohort studies. Studies suggest that the risk of diverticulitis may be further reduced with exercise and avoidance of red meats and NSAIDs.

Ma W et al. Intake of dietary fiber, fruits, and vegetables and risk of diverticulitis. Am J Gastroenterol. 2019;114:1531. [PMID: 31397679]
Strate LL et al. Epidemiology, pathophysiology, and treatment of diverticulitis. Gastroenterology. 2019;156:1282. [PMID: 30660732]

2. Diverticulitis

ESSENTIALS OF DIAGNOSIS

- Acute abdominal pain and fever.
- Left lower abdominal tenderness and mass.
- Leukocytosis.

Clinical Findings

A. Symptoms and Signs

Diverticulitis is defined as macroscopic inflammation of a diverticulum that may reflect a spectrum from inflammation

alone, to microperforation with localized paracolic inflammation, to macroperforation with either abscess or generalized peritonitis. Thus, there is a range from mild to severe disease. Most patients with localized inflammation or infection report mild to moderate aching abdominal pain, usually in the left lower quadrant. Constipation or loose stools may be present. Nausea and vomiting are frequent. In many cases, symptoms are so mild that the patient may not seek medical attention until several days after onset. Physical findings include a low-grade fever, left lower quadrant tenderness, and a palpable mass. Stool occult blood is common, but hematochezia is rare. Leukocytosis is mild to moderate. Patients with free perforation present with a more dramatic picture of generalized abdominal pain and peritoneal signs.

B. Imaging

In those presenting for the first time with mild symptoms, an abdominal CT is obtained to look for evidence of diverticulitis (colonic diverticula, wall thickening, pericolic fat infiltration) and to exclude other causes of abdominal pain. An abdominal CT is also indicated in patients with fever, leukocytosis, and sepsis or peritonitis or in those who are immunocompromised to look for evidence of complicated disease (abscess, phlegmon, perforation, fistula). Patients who respond to acute medical management should undergo complete colonic evaluation with colonoscopy or CT colonography 6–8 weeks after resolution of clinical symptoms to exclude colorectal cancer (which may mimic diverticulitis). Cancer is identified in 1.3% and 7.9% of patients following a diagnosis of uncomplicated or complicated diverticulitis, respectively. Endoscopy and colonography are contraindicated during the initial stages of an acute attack because of the risk of free perforation.

Differential Diagnosis

Diverticulitis must be distinguished from other causes of lower abdominal pain, including perforated colonic carcinoma, Crohn disease, appendicitis, ischemic colitis, *C difficile*–associated colitis, and gynecologic disorders (ectopic pregnancy, ovarian cyst or torsion), by abdominal CT scan, pelvic ultrasonography, or radiographic studies of the distal colon that use water-soluble contrast enemas.

Complications

Complications, such as phlegmon, abscess, perforation, peritonitis, or sepsis, develop in approximately 12% of patients with acute diverticulitis. Chronic inflammation or an untreated abscess may lead to smoldering disease (ongoing pain, leukocytosis); formation of fistulas to the bladder, ureter, vagina, uterus, bowel, and abdominal wall; or stricturing of the colon with partial or complete obstruction.

Treatment

A. Medical Management

Most patients with uncomplicated disease can be managed with conservative measures. Patients with mild symptoms and no peritoneal signs may be managed initially as outpatients on a clear liquid diet for 2–3 days. Although broad-spectrum oral antibiotics with anaerobic activity commonly are prescribed, large clinical trials confirm that antibiotics are not beneficial in uncomplicated disease. A 2021 AGA guideline suggests that antibiotics should be used selectively for uncomplicated disease, including patients who are immunocompromised, have significant comorbid disease, or have small pericolonic abscesses (less than 3–4 cm). Reasonable regimens include amoxicillin and clavulanate potassium (875 mg/125 mg) twice daily; or metronidazole, 500 mg three times daily plus either ciprofloxacin, 500 mg twice daily, or trimethoprim-sulfamethoxazole, 160/800 mg twice daily orally, for 7–10 days or until the patient is afebrile for 3–5 days. Symptomatic improvement usually occurs within 3 days, at which time the diet may be advanced. Once the acute episode has resolved, a high-fiber diet is recommended.

Patients with increasing pain, fever, or inability to tolerate oral fluids require hospitalization. Hospitalization is required in patients who are immunocompromised, have significant comorbid illness, have abscesses greater than 3–4 cm, or have signs of severe diverticulitis (high fevers, leukocytosis, or peritoneal signs). Patients should be given nothing by mouth and should receive intravenous fluids. If ileus is present, a nasogastric tube should be placed. Intravenous antibiotics should be given to cover anaerobic and gram-negative bacteria. Single-agent therapy with either a second-generation cephalosporin (eg, cefoxitin), piperacillin-tazobactam, or ticarcillin clavulanate appears to be as effective as combination therapy (eg, metronidazole or clindamycin plus an aminoglycoside or third-generation cephalosporin [eg, ceftazidime, cefotaxime]). Symptomatic improvement should be evident within 2–3 days. Intravenous antibiotics should be continued for 5–7 days, before changing to oral antibiotics.

B. Surgical Management

Surgical consultation and repeat abdominal CT should be obtained on all patients with severe disease or those who do not improve after 72 hours of medical management. Patients with a localized abdominal abscess 4 cm in size or larger are usually treated urgently with a percutaneous catheter drain placed by an interventional radiologist. This permits control of the infection and resolution of the immediate infectious inflammatory process. Indications for emergent surgical management include generalized peritonitis, large undrainable abscesses, and clinical deterioration despite medical management and percutaneous drainage. Following recovery from complicated diverticulitis, a subsequent elective one-stage surgical resection has generally been recommended to reduce recurrent episodes of complicated disease; however, a conservative approach may be selected for some patients. Patients with chronic disease resulting in fistulas or colonic obstruction will require elective surgical resection.

Prognosis

Diverticulitis recurs in 15–20% of patients treated with medical management over 10–20 years. However, less than

5% have more than two recurrences. Among patients who have an episode of uncomplicated diverticulitis, less than 5% later develop complicated disease. Therefore, elective surgical resection is no longer routinely recommended in patients with recurrent bouts of uncomplicated disease but is individualized based on patient preference, age, comorbid disease, and frequency and severity of attacks. Diverticulosis is not associated with an increased risk of colorectal cancer.

When to Refer

- Failure to improve within 72 hours of medical management.
- Presence of significant peridiverticular abscesses (4 cm or larger) requiring possible percutaneous or surgical drainage.
- Generalized peritonitis or sepsis.
- Recurrent attacks.
- Chronic complications, including colonic strictures or fistulas.

When to Admit

- Severe pain or inability to tolerate oral intake.
- Signs of sepsis or peritonitis.
- CT showing signs of complicated disease (abscess, perforation, obstruction).
- Failure to improve with outpatient management.
- Immunocompromised or frail, older patient.

Hall J et al. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the treatment of left-sided colonic diverticulitis. Dis Colon Rectum. 2020;63:728. [PMID: 32384404]

Jaung R et al. Antibiotics do not reduce length of hospital stay for uncomplicated diverticulitis in a pragmatic double-blind randomized trial. Clin Gastroenterol Hepatol. 2021;19:503. [PMID: 32240832]

Peery AF et al. AGA clinical practice update on medical management of colonic diverticulitis: expert review. Gastroenterology. 2021;160:906. [PMID: 33279517]

Tehranian S et al. Prevalence of colorectal cancer and advanced adenoma in patients with acute diverticulitis: implications for follow up colonoscopy. Gastrointest Endosc. 2020;91:634. [PMID: 31521778]

3. Diverticular Bleeding

Half of all cases of acute lower GI bleeding are attributable to diverticulosis (see Acute Lower GI Bleeding, above).

POLYPS OF THE COLON

Polyps are discrete mass lesions that protrude into the intestinal lumen. Although most commonly sporadic, they may be inherited as part of a familial polyposis syndrome. Polyps may be divided into four major pathologic groups: mucosal adenomatous polyps (tubular, tubulovillous, and villous), mucosal serrated polyps (hyperplastic, sessile serrated polyps, and traditional serrated adenoma), mucosal nonneoplastic polyps (juvenile polyps, hamartomas, inflammatory polyps), and submucosal lesions (lipomas, lymphoid aggregates, carcinoids, pneumatosis cystoides intestinalis). Of polyps removed at colonoscopy, over 70% are adenomatous; most of the remainder are serrated.

NONFAMILIAL ADENOMATOUS & SERRATED POLYPS

Adenomas and serrated polyps may be non-polypoid (flat, slightly elevated, or depressed), sessile, or pedunculated (containing a stalk). Their significance is that over 95% of cases of adenocarcinoma of the colon are believed to arise from these lesions. Early detection and removal of these precancerous lesions through screening programs has resulted in a 34% reduction in deaths from colorectal cancer since 2000. It is proposed that there is a polyp → carcinoma sequence whereby nonfamilial colorectal cancer develops through a continuous process from normal mucosa to adenomatous or serrated polyp and later to carcinoma. An estimated 75% of cancers arise in adenomas after inactivation of the *APC* gene leads to chromosomal instability and inactivation or loss of other tumor suppressor genes. The remaining 25% of cancers arise through the serrated pathway in which hyperplastic polyps develop *Kras* mutations (forming traditional serrated adenomas) or *BRAF* oncogene activation (forming sessile serrated lesions) with widespread methylation of CpG-rich promoter regions that leads to inactivation of tumor suppressor genes or mismatch repair genes (*MLH1*) with microsatellite instability.

A. Adenomas

Adenomas are present in more than 30% of men and 20% of women over the age of 50. Most adenomas are smaller than 5 mm and have a low risk of becoming malignant. Adenomas are classified as "advanced" if they are 1 cm or larger or contain villous features or high-grade dysplasia. In the general population, the prevalence of advanced adenomas is 6%. Advanced lesions are believed to have a higher risk of harboring or progressing to malignancy. It has been estimated from longitudinal studies that it takes an average of 5 years for a medium-sized polyp to develop from normal-appearing mucosa and 10 years for a gross cancer to arise.

B. Serrated Polyps

There are three types of serrated polyps: hyperplastic polyps, sessile serrated lesions, and traditional serrated adenomas. It is believed that sessile serrated lesions (prevalence 5–12%) and traditional serrated adenomas (prevalence less than 1%) entail an increased risk of colorectal cancer similar or greater to that of adenomas and account for up to 20–30% of colorectal cancers. Many pathologists cannot reliably distinguish between hyperplastic polyps and sessile serrated lesions. Diminutive hyperplastic polyps (less than 5 mm) are extremely common (prevalence 20–30%), especially in the rectum, and believed to be without significant risk.

Clinical Findings

A. Symptoms and Signs

Most patients with adenomatous and serrated polyps are completely asymptomatic. Chronic occult blood loss may lead to iron deficiency anemia. Large polyps may ulcerate, resulting in intermittent hematochezia.

B. Fecal Occult Blood or Multitarget DNA Tests

FOBT, FIT, and fecal DNA tests are available as part of colorectal cancer screening programs (see Chapter 39). FIT is a fecal immunochemical test for hemoglobin with a single specimen having a sensitivity of approximately 80% for colorectal cancer and 20–30% for advanced adenomas but a much lower sensitivity for serrated lesions. FIT is more sensitive than guaiac-based tests for the detection of colorectal cancer and advanced adenomas. In 2014, a test combining a fecal DNA test with a fecal immunochemical test for stool hemoglobin (under the proprietary name "Cologuard") was approved by the FDA. In a prospective comparative trial conducted in persons at average risk for colorectal cancer undergoing colonoscopy, the sensitivity for colorectal cancer for Cologuard was 92.3% compared to 73.8% for FIT and the sensitivity for large (greater than 1 cm) adenomas or serrated polyps for Cologuard was 42.4% compared to 23.8% for FIT.

C. Radiologic Tests

CT colonography ("virtual colonoscopy") uses data from helical CT with computer-enabled luminal image reconstruction to generate two-dimensional and three-dimensional images of the colon. Using optimal imaging software with multidetector helical CT scanners, several studies report a sensitivity of 90% or more for the detection of polyps larger than 10 mm in size. However, the accuracy for detection of polyps 5–9 mm in size is significantly lower (sensitivity 50%). A small proportion of these diminutive polyps harbor advanced histology (up to 1.2%) or carcinoma (less than 1%). Abdominal CT also results in a radiation exposure that may lead to a small risk of cancer.

D. Endoscopic Tests

Colonoscopy allows evaluation of the entire colon and is the best means of detecting and removing adenomatous and serrated polyps. It should be performed in all patients who have positive FOBT, FIT, or fecal DNA tests or iron deficiency anemia (see Occult GI Bleeding above) since the prevalence of colonic neoplasms is increased in these patients. Colonoscopy should also be performed in patients with polyps detected on CT colonography or adenomas detected on flexible sigmoidoscopy to remove these polyps and to fully evaluate the entire colon. The newest generation of capsule endoscopy of the colon has an 86% sensitivity and 88% specificity for detection of adenomas greater than 6 mm compared with colonoscopy, but only 29% sensitivity and 33% specificity for sessile serrated polyps. Capsule endoscopy may be considered in patients who are unsuitable or unwilling to undergo colonoscopy or who have an incomplete colonoscopy.

Treatment

A. Colonoscopic Polypectomy

Most adenomatous and serrated polyps are less than 2 cm in size and are readily amenable to colonoscopic removal; this can be done with biopsy forceps (for those less than 3 mm), with cold snare excision (for those less than 10 mm), or with cold snare or hot snare cautery (for those 10–20 mm). Sessile polyps larger than 2 cm may be removed by appropriately trained physicians using a variety of endoscopic techniques (eg, saline-lift mucosal resection or dissection) or infrequently may require surgical resection. Patients with large sessile polyps removed in piecemeal fashion should undergo repeated colonoscopy in 6 months to verify complete polyp removal. Complications after colonoscopic polypectomy include perforation in 0.2% and clinically significant bleeding in 0.3–1.0% of all patients, but in 4–8% following mucosal resection of large lesions.

B. Postpolypectomy Surveillance

Adenomas and serrated polyps can be found in 30–40% of patients when another colonoscopy is performed within 3–5 years after the initial examination and polyp removal. Periodic colonoscopic surveillance is therefore recommended to detect these "metachronous" lesions, which either may be new or may have been overlooked during the initial examination. Most of these polyps are small, without high-risk features, and of little immediate clinical significance. The probability of detecting advanced neoplasms at surveillance colonoscopy depends on the number, size, and histologic features of the polyps removed on initial (index) colonoscopy. The US Multi-Society Task Force Guideline provides the following recommendations for repeat colonoscopy that depend on the findings at baseline colonoscopy: (1) **10 years:** normal colonoscopy or fewer than 20 hyperplastic polyps less than 10 mm in the distal colon or rectum; (2) **7–10 years:** 1–2 adenomas less than 10 mm; (3) **5–10 years**: 1–2 sessile serrated polyps less than 10 mm; (4): **3–5 years:** 3–4 adenomas or sessile serrated polyps less than 10 mm; (5) **3 years:** 5–10 adenomas *or* sessile serrated polyps less than 10 mm; *or* 1 or more adenomas or sessile serrated polyp 10 mm or larger *or* an adenoma containing villous features or high-grade dysplasia *or* a sessile serrated polyp with dysplasia. Patients with more than 10 adenomas should have a repeat colonoscopy at 1 year and may be considered for evaluation for a familial polyposis syndrome.

Gupta S et al. Recommendations for follow-up after colonoscopy and polypectomy: a consensus updated by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2020;158:1131. [PMID: 32039982]

Kaltenbach T et al. Endoscopic removal of colorectal lesions—recommendations of the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2020;158:1095. [PMID: 32058340]

Meester RG et al. Prevalence and clinical features of sessile serrated polyps: a systematic review. Gastroenterology. 2020;159:105. [PMID: 32199884]

HEREDITARY COLORECTAL CANCER & POLYPOSIS SYNDROMES

Up to 4% of all colorectal cancers are caused by germline genetic mutations that impose on carriers a high lifetime risk of developing colorectal cancer (see Chapter 39). Because the diagnosis of these disorders has important implications for treatment of affected patients and for screening of family members, it is important to consider these disorders in patients with a family history of colorectal cancer that has affected more than one family member, those with a personal or family history of colorectal cancer developing at an early age (50 years or younger), those with a personal or family history of multiple polyps (more than 10), and those with a personal or family history of multiple extracolonic malignancies.

1. Familial Adenomatous Polyposis

ESSENTIALS OF DIAGNOSIS

- Inherited condition characterized by early development of hundreds to thousands of colonic adenomatous polyps.
- Variety of extracolonic manifestations (eg, duodenal adenomas, desmoid tumors, and osteomas) and extracolonic cancers (stomach, duodenum, thyroid).
- Attenuated variant with < 100 (average 25) colonic adenomas.
- Genetic testing confirms mutation of *APC* gene (90%) or *MUTYH* gene (8%).
- Prophylactic colectomy recommended to prevent otherwise inevitable colorectal cancer (adenocarcinoma).

General Considerations

Familial adenomatous polyposis (FAP) is a syndrome affecting 1:10,000 people and accounts for approximately 0.5% of colorectal cancers. The classic form of FAP is characterized by the development of hundreds to thousands of colonic adenomatous polyps and a variety of extracolonic manifestations. Of patients with classic FAP, approximately 90% have a mutation in the *APC* gene that is inherited in an autosomal dominant fashion and 8% have mutations in the *MUTYH* gene that are inherited in an autosomal recessive fashion. FAP arises de novo in 25% of patients in the absence of genetic mutations in the parents. An attenuated variant of FAP also has been recognized in which an average of only 25 polyps (range of 1–100) develop.

Clinical Findings

A. Symptoms and Signs

In classic FAP, colorectal polyps develop by a mean age of 15 years and cancer often by age 40 years. Unless prophylactic colectomy is performed, colorectal cancer is inevitable by age 50 years. In attenuated FAP, the mean age for development of cancer is about 56 years.

Adenomatous polyps of the duodenum and periampullary area develop in over 90% of patients, resulting in a 5–8% lifetime risk of adenocarcinoma. Adenomas occur less frequently in the gastric antrum and small bowel and, in those locations, have a lower risk of malignant transformation. Gastric fundus gland polyps occur in over 50% but have an extremely low (0.6%) malignant potential.

A variety of other benign extraintestinal manifestations, including soft tissue tumors of the skin, desmoid tumors, osteomas, and congenital hypertrophy of the retinal pigment, develop in some patients with FAP. These extraintestinal manifestations vary among families, depending in part on the type or site of mutation in the *APC* gene. Desmoid tumors are locally invasive fibromas, most commonly intra-abdominal, that may cause bowel obstruction, ischemia, or hemorrhage. They occur in 15% of patients and are the second leading cause of death in FAP. Malignancies of the CNS (Turcot syndrome) and tumors of the thyroid and liver (hepatoblastomas) may also develop in patients with FAP.

B. Genetic Testing

Genetic counseling and testing should be offered to patients found to have multiple adenomatous polyps at endoscopy and to first-degree family members of patients with FAP. Most centers now perform genetic testing using a multigene panel of 14–67 hereditary cancer genes, including *APC* and *MUTYH*. *APC* gene mutations are identified in 80% of patients with more than 1000, and 56% with 100–1000 polyps (ie, the classic phenotype of FAP). Current guidelines recommend that genetic testing be considered in individuals with as few as 10 adenomas to exclude a diagnosis of attenuated disease, most especially in patients less than age 50–60 years.

Treatment

Once the diagnosis has been established, complete proctocolectomy with ileoanal anastomosis or colectomy with ileorectal anastomosis is recommended in most patients, usually before age 20 years. Colonoscopy every 1–2 years with polypectomy may be considered for patients with attenuated FAP and a low number of polyps. Upper endoscopic evaluation of the stomach, duodenum, and periampullary area should be performed every 1–3 years to look for adenomas or carcinoma with resection of duodenal or ampullary polyps greater than 10 mm, increasing in size, or suspicious for high-grade dysplasia or cancer. Sulindac and celecoxib have been shown to decrease the number and size of polyps in the rectal stump but not the duodenum.

Kupfer SS et al. Patients in whom to consider genetic evaluation and testing for hereditary colorectal cancer syndromes. Am J Gastroenterol. 2020;115:1. [PMID: 31634263]

Yang J et al. American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in familial adenomatous polyposis syndromes. Gastrointest Endosc. 2020;91:963. [PMID: 32169282]

2. Hamartomatous Polyposis Syndromes

Hamartomatous polyposis syndromes are rare and account for less than 0.1% of colorectal cancers. They include Peutz-Jeghers syndrome, familial juvenile polyposis, and Cowden disease.

Tacheci I et al. Peutz-Jeghers syndrome. Curr Opin Gastroenterol. 2021;37:245. [PMID: 33591027]
Wagner A et al. The management of Peutz-Jeghers syndrome: European Hereditary Tumour Group (EHTG) guideline. J Clin Med. 2021;10:473. [PMID: 33513864]

3. Lynch Syndrome

ESSENTIALS OF DIAGNOSIS

- Autosomal dominant inherited condition.
- Caused by pathogenic variants in a gene that detects and repairs DNA base-pair mismatches, resulting in DNA microsatellite instability and inactivation of tumor suppressor genes.
- Increased lifetime risk of colorectal cancer (22–75%), endometrial cancer (30–60%), and other cancers; they may develop at young ages.
- Evaluation warranted in patients with personal history of early-onset colorectal cancer or family history of colorectal, endometrial, or other Lynch syndrome–related cancers at young age or in multiple family members.
- Diagnosis suspected by tumor tissue immunohistochemical staining for mismatch repair proteins or by testing for microsatellite instability.
- Diagnosis confirmed by genetic testing.

General Considerations

Lynch syndrome (also known as hereditary nonpolyposis colon cancer [HNPCC]) is an autosomal dominant condition in which there is a markedly increased risk of developing colorectal cancer as well as a host of other cancers, including endometrial, ovarian, kidney, bladder, hepatobiliary, gastric, and small intestinal cancers. It is estimated to account for up to 3% of all colorectal cancers. Affected individuals have a 22–75% lifetime risk of developing colorectal carcinoma and a 30–60% lifetime risk of endometrial cancer, depending on the variant gene. Unlike individuals with familial adenomatous polyposis, patients with Lynch syndrome develop only a few adenomas, which may be flat and more often contain villous features or high-grade dysplasia. In contrast to the traditional polyp → cancer progression (which may take over 10 years), these polyps are believed to undergo rapid transformation over 1–2 years from normal tissue → adenoma → cancer. Colon and endometrial cancer tend to develop at an earlier age (mean age 45–50 years) than sporadic, nonhereditary cancers. A germline pathogenic variant is identified in 20% of patients in whom colon cancer was diagnosed before age 50. Compared to patients with sporadic tumors of similar pathologic stage, those with Lynch syndrome tumors have improved survival. However, synchronous or metachronous cancers occur within 10 years in up to 45% of patients.

Lynch syndrome is caused by a defect in one of several genes that are important in the detection and repair of DNA base-pair mismatches: *MLH1, MSH2, MSH6,* and *PMS2* or EPCAM, a promoter for *MSH2*. Germline pathogenic variants in *MLH1* and *MSH2* account for almost 90% of the known variants in families with Lynch syndrome. Variants in any of these mismatch repair genes result in a characteristic phenotypic DNA abnormality known as microsatellite instability.

Clinical Findings

A thorough family cancer history is essential to identify families that may be affected by the Lynch syndrome so that appropriate genetic and colonoscopic screening can be offered. The National Colorectal Cancer Roundtable recommends a simple three-question tool for identifying increased risk and meriting more detailed assessment: (1) Have you had colorectal cancer or polyps diagnosed before age 50? (2) Do you have three or more relatives with colorectal cancer? and (3) Do you have a first-degree relative with colorectal cancer or another Lynch syndrome–related cancer diagnosed before age 50? The PREMM5 probability model is available for calculating the likelihood of Lynch syndrome based on family and personal history (https://premm.dfci.harvard.edu/). Genetic evaluation is recommended for those with a personal or family history of colorectal cancer under age 50, a history of multiple family members with cancer, or a greater than 5% PREMM5 model-predicted chance of Lynch syndrome. Genetic testing can be performed with multigene panels that test for germline cancer genes (ie, Lynch, familial adenomatous polyposis, and hamartomatous syndromes) as well as others of uncertain significance for approximately $250. Referral to a genetic counselor is recommended.

Personal and family history alone are insufficient to identify a significant proportion of patients with Lynch syndrome. For this reason, the National Comprehensive Cancer Network recommend that *all* colorectal cancers should undergo testing for Lynch syndrome with either immunohistochemistry or microsatellite instability. Universal testing has the greatest sensitivity for the diagnosis of Lynch syndrome and is cost-effective. Individuals whose tumors have normal immunohistochemical staining or do not have microsatellite instability are unlikely to have germline pathogenic variants in mismatch repair genes, do not require further genetic testing, and do not require intensive cancer surveillance. Up to 15% of sporadic (noninherited) tumors have microsatellite instability or absent *MLH1* staining due to somatic (noninherited) methylation of the *MLH1* gene promoter and somatic *BRAF* mutations, which must be excluded before further genetic testing is considered. Germline testing for gene mutations is positive in more than 90% of individuals whose tumors show absent histochemical staining of one of the mismatch repair genes or high level of microsatellite instability without a *BRAF* mutation.

Screening & Treatment

If a pathogenic variant is detected in a patient with cancer in one of the known mismatch genes, genetic testing of other first-degree family members is indicated. If genetic testing documents a Lynch syndrome gene variant, affected relatives should be screened with colonoscopy every 1–2 years beginning at age 25 (or at age 5 years younger than the age at diagnosis of the youngest affected family member). If cancer is found, subtotal colectomy with ileorectal anastomosis (followed by annual surveillance of the rectal stump) should be performed. Women should undergo screening for endometrial and ovarian cancer beginning at age 30–35 years with pelvic examination, transvaginal ultrasound, and endometrial sampling. Prophylactic hysterectomy and oophorectomy are recommended to women at age 40 or once they have finished childbearing. Screening for gastric cancer with upper endoscopy should be considered every 2–3 years beginning at age 30–35 years.

Biller LH et al. Familial burden and other clinical factors associated with various types of cancer in individuals with Lynch syndrome. Gastroenterology. 2021;161:143. [PMID: 33794268]
Ladabaum U. What is Lynch-like syndrome and how should we manage it? Clin Gastroenterol Hepatol. 2020;18:294. [PMID: 31408703]
Xi L et al. Recent advances in Lynch syndrome. Exp Hematol Oncol. 2021;10:37. [PMID: 34118983]

ANORECTAL DISEASES

(See Chapter 39 **for Carcinoma of the Anus.)**

HEMORRHOIDS

ESSENTIALS OF DIAGNOSIS

- Bright red blood per rectum.
- Protrusion, discomfort.
- Characteristic findings on external anal inspection and anoscopic examination.

General Considerations

Internal hemorrhoids are subepithelial vascular cushions consisting of connective tissue, smooth muscle fibers, and arteriovenous communications between terminal branches of the superior rectal artery and rectal veins. They are a normal anatomic entity, occurring in all adults, that contribute to normal anal pressures and ensure a water-tight closure of the anal canal. They commonly occur in three primary locations—right anterior, right posterior, and left lateral. External hemorrhoids arise from the inferior hemorrhoidal veins located below the dentate line and are covered with squamous epithelium of the anal canal or perianal region.

Hemorrhoids may become symptomatic as a result of activities that increase venous pressure, resulting in distention and engorgement. Straining at stool, diarrhea, constipation, prolonged sitting, pregnancy, obesity, and low-fiber diets all may contribute. With time, redundancy and enlargement of the venous cushions may develop and result in bleeding or protrusion.

Clinical Findings

A. Symptoms and Signs

Patients often attribute a variety of perianal complaints to "hemorrhoids." However, the principal problems attributable to internal hemorrhoids are bleeding, prolapse, and mucoid discharge. Bleeding is manifested by bright red blood that may range from streaks of blood visible on toilet paper or stool to bright red blood that drips into the toilet bowl after a bowel movement. Uncommonly, bleeding is severe and prolonged enough to result in anemia. Initially, internal hemorrhoids are confined to the anal canal (stage I). Over time, the internal hemorrhoids may gradually enlarge and protrude from the anal opening. At first, this mucosal prolapse occurs during straining and reduces spontaneously (stage II). With progression over time, the prolapsed hemorrhoids may require manual reduction after bowel movements (stage III) or may remain chronically protruding (stage IV). Chronically prolapsed hemorrhoids may result in a sense of fullness or discomfort and mucoid discharge, resulting in irritation of perianal skin and soiling of underclothes. Pain is unusual with internal hemorrhoids, occurring only when there is extensive inflammation and thrombosis of irreducible tissue or with thrombosis of an external hemorrhoid.

B. Examination

External hemorrhoids are readily visible on perianal inspection. Nonprolapsed internal hemorrhoids are not visible but may protrude through the anus with gentle straining while the clinician spreads the buttocks. Prolapsed hemorrhoids are visible as protuberant purple nodules covered by mucosa. The perianal region should also be examined for other signs of disease such as fistulas, fissures, skin tags, condyloma, anal cancer, or dermatitis. On digital examination, uncomplicated internal hemorrhoids are neither palpable nor painful. Anoscopic evaluation, best performed in the prone jackknife position, provides optimal visualization of internal hemorrhoids.

Differential Diagnosis

Small volume rectal bleeding may be caused by an anal fissure or fistula, neoplasms of the distal colon or rectum, ulcerative colitis or Crohn colitis, infectious proctitis, or rectal ulcers. Rectal prolapse, in which a full thickness of rectum protrudes concentrically from the anus, is readily distinguished from mucosal hemorrhoidal prolapse. Proctosigmoidoscopy or colonoscopy should be performed in all patients with hematochezia to exclude disease in the rectum or sigmoid colon that could be misinterpreted in the presence of hemorrhoidal bleeding.

Treatment

A. Conservative Measures

Most patients with early (stage I and stage II) disease can be managed with conservative treatment. To decrease straining with defecation, patients should be given instructions for a high-fiber diet and told to increase fluid intake with meals, avoid straining, and limit sitting time on the toilet to less than 5 minutes. Dietary fiber may be supplemented with bran powder (1–2 tbsp twice daily added to food or in 8 oz of liquid) or with commercial bulk laxatives (eg, Benefiber, Metamucil, Citrucel). Suppositories and rectal ointments have no demonstrated utility in the management of mild disease. Mucoid discharge may be treated effectively by the local application of a cotton ball tucked next to the anal opening after bowel movements.

B. Medical Treatment

Patients with stage I, stage II, and stage III hemorrhoids and recurrent bleeding despite conservative measures may be treated without anesthesia with rubber band ligation, injection sclerotherapy, or application of electrocoagulation (bipolar cautery or infrared photocoagulation). The choice of therapy is dictated by operator preference, but rubber band ligation is preferred due to its ease of use and high rate of efficacy. Major complications occur in less than 2%, including pelvic sepsis, pelvic abscess, urinary retention, and bleeding. Recurrence is common unless patients alter their dietary habits. Edematous, prolapsed (stage IV) internal hemorrhoids, may be treated acutely with topical creams, foams, or suppositories containing various combinations of emollients, topical anesthetics, (eg, pramoxine, dibucaine), vasoconstrictors (eg, phenylephrine), astringents (witch hazel), and corticosteroids. Common preparations include Preparation H (several formulations), Anusol HC, Proctofoam, Nupercainal, Tucks, and Doloproct (not available in the United States).

C. Surgical Treatment

Surgical excision (traditional hemorrhoidectomy or stapled hemorrhoidopexy) is reserved for less than 5–10% of patients with chronic severe bleeding due to stage III or stage IV hemorrhoids or patients with acute thrombosed stage IV hemorrhoids with necrosis. Complications of surgical hemorrhoidectomy include postoperative pain (which may persist for 2–4 weeks) and impaired continence.

Thrombosed External Hemorrhoid

Thrombosis of the external hemorrhoidal plexus results in a perianal hematoma. It most commonly occurs in otherwise healthy young adults and may be precipitated by coughing, heavy lifting, or straining at stool. The condition is characterized by the relatively acute onset of an exquisitely painful, tense and bluish perianal nodule covered with skin that may be up to several centimeters in size. Pain is most severe within the first few hours but gradually eases over 2–3 days as edema subsides. Symptoms may be relieved with warm sitz baths, analgesics, and ointments. With symptom resolution, a perianal skin tag may persist, which can be a source of irritation. If the patient is evaluated in the first 24–48 hours, removal of the clot may hasten symptomatic relief. With the patient in the lateral position, the skin around and over the lump is injected subcutaneously with 1% lidocaine using a tuberculin syringe with a 30-gauge needle. An ellipse of skin is then excised and the clot evacuated. A dry gauze dressing is applied for 12–24 hours, and daily sitz baths are then begun.

When to Refer

- Stage I, II, or III: When conservative measures fail and expertise in medical procedures is needed (injection, banding, thermocoagulation).
- Stage IV: When surgical therapy is required.

Gardner IH et al. Benign anorectal disease: hemorrhoids, fissures, and fistulas. Ann Gastroenterol. 2020;33:9. [PMID: 31892792]
Muldoon R. Review of American Society of Colon and Rectal Surgeons clinical practice guidelines for the management of hemorrhoids. JAMA Surg. 2020;155:773. [PMID: 32584937]
Wald A et al. ACG Clinical guideline: management of benign anorectal disorders. Am J Gastroenterol. 2021;116:1987. [PMID: 34618700]

ANORECTAL INFECTIONS

A number of organisms can cause inflammation of the anal and rectal mucosa. Proctitis is characterized by anorectal discomfort, tenesmus, constipation, and mucus or bloody discharge. Most cases of proctitis are sexually transmitted, especially by anal-receptive intercourse. Infectious proctitis must be distinguished from noninfectious causes of anorectal symptoms, including anal fissures or fistulae, perirectal abscesses, anorectal carcinomas, and inflammatory bowel disease (ulcerative colitis or Crohn disease).

Etiology & Management

Several organisms may cause infectious proctitis.

A. *Neisseria gonorrhoeae*

Gonorrhea may cause itching, burning, tenesmus, and a mucopurulent discharge, although many anorectal infections are asymptomatic. Nucleic acid amplification testing for gonorrhea and chlamydia has excellent sensitivity and specificity and is preferred in most clinical settings due to ease of transport and laboratory processing. Rectal swab specimens should be taken during anoscopy. Swabs should also be taken from the pharynx and urethra in men and from the pharynx and cervix in women. Culture with sensitivity testing may be required in patients with suspected infection recurrence. Complications of untreated infections include strictures, fissures, fistulas, and perirectal abscesses. (For treatment, see Chapter 33.)

B. *Treponema pallidum*

Anal syphilis may be asymptomatic or may lead to perianal pain and discharge. With primary syphilis, the chancre

may be at the anal margin or within the anal canal and may mimic a fissure, fistula, or ulcer. Proctitis or inguinal lymphadenopathy may be present. With secondary syphilis, condylomata lata (pale-brown, flat verrucous lesions) may be seen, with secretion of foul-smelling mucus. Although the diagnosis may be established with dark-field microscopy or fluorescent antibody testing of scrapings from the chancre or condylomas, this requires proper equipment and trained personnel. The VDRL or RPR test is positive in 75% of primary cases and in 99% of secondary cases. (For treatment, see Chapter 34.)

C. *Chlamydia trachomatis*

Chlamydial infection may cause proctitis similar to gonorrheal proctitis; however, some infections are asymptomatic. It also may cause lymphogranuloma venereum, characterized by proctocolitis with fever and bloody diarrhea, painful perianal ulcerations, anorectal strictures and fistulas, and inguinal adenopathy (buboes). Previously rare in developed countries, an increasing number of cases have been identified among men who have sex with men. The diagnosis is established by PCR-based testing of rectal discharge or rectal biopsy. Recommended treatment is doxycycline 100 mg orally twice daily for 21 days.

D. Herpes Simplex Type 2

Herpes simplex type 2 virus is a common cause of anorectal infection. Symptoms occur 4–21 days after exposure and include severe pain, itching, constipation, tenesmus, urinary retention, and radicular pain from involvement of lumbar or sacral nerve roots. Small vesicles or ulcers may be seen in the perianal area or anal canal. Sigmoidoscopy is not usually necessary but may reveal vesicular or ulcerative lesions in the distal rectum. Diagnosis is established by viral culture, PCR, or antigen detection assays of vesicular fluid. Symptoms resolve within 2 weeks, but viral shedding may continue for several weeks. Patients may remain asymptomatic with or without viral shedding or may have recurrent mild relapses. Treatment of acute infection for 7–10 days with acyclovir, 400 mg, or famciclovir, 250 mg orally three times daily, or valacyclovir, 1 g twice daily, has been shown to reduce the duration of symptoms and viral shedding. Patients with AIDS and recurrent relapses may benefit from long-term suppressive therapy (see Chapter 31).

E. Condylomata Acuminata

Condylomata acuminata (warts) are a significant cause of anorectal symptoms. Caused by the HPV, they may occur on the perianal area, in the anal canal, or on the genitals. Perianal or anal warts are seen in up to 25% of men who have sex with men. HIV-positive individuals with condylomas have a higher relapse rate after therapy and a higher rate of progression to high-grade dysplasia or anal cancer. The warts are located on the perianal skin and extend within the anal canal up to 2 cm above the dentate line. Patients may have no symptoms or may report itching, bleeding, and pain. The warts may be small and flat or verrucous, or may form a confluent mass that may obscure the anal opening. Warts must be distinguished from condyloma lata (secondary syphilis) or anal cancer. Biopsies should be obtained from large or suspicious lesions. Treatment can be difficult. Sexual partners should also be examined and treated. The treatment of anogenital warts is discussed in Chapter 30. The HPV vaccine, Gardasil-9 valent, has demonstrated efficacy in preventing anogenital warts and is now recommended for all persons aged 9–14 (two or three doses) and persons aged 15–45 (three doses), as well as all men of any age who have sex with men (see Chapters 1 and 30). HIV-positive individuals with condylomas who have detectable serum HIV RNA levels should have anoscopic surveillance for anal cancer every 3–6 months.

Blanco JL et al. Effective treatment of lymphogranuloma venereum proctitis with azithromycin. Clin Infect Dis. 2021;73:614. [PMID: 33462582]
Davidson KW et al. Screening for chlamydia and gonorrhea: US Preventive Services Task Force recommendations statement. JAMA. 2021;326:949. [PMID: 34519796]
Workowski KA et al. Sexually transmitted infection treatment guidelines, 2021. MMWR Recomm Rep. 2021;70:1. [PMID: 34292926]

FECAL INCONTINENCE

In a 2018 survey, 4.7% of US adults reported fecal incontinence within the prior 30 days. There are five general requirements for bowel continence: (1) solid or semisolid stool (even healthy young adults have difficulty maintaining continence with liquid rectal contents); (2) a distensible rectal reservoir (as sigmoid contents empty into the rectum, the vault must expand to accommodate); (3) a sensation of rectal fullness (if the patient cannot sense this, overflow may occur before the patient can take appropriate action); (4) intact pelvic nerves and muscles; and (5) the ability to reach a toilet in a timely fashion.

Minor Incontinence

Many patients complain of inability to control flatus or slight soilage of undergarments that tends to occur after bowel movements or with straining or coughing. This may be due to local anal problems such as prolapsed hemorrhoids that make it difficult to form a tight anal seal or isolated weakness of the internal anal sphincter, especially if stools are somewhat loose. Patients should be treated with fiber supplements to provide greater stool bulk. Coffee and other caffeinated beverages should be eliminated. The perianal skin should be cleansed with moist, lanolin-coated tissue (baby wipes) to reduce excoriation and infection. After wiping, loose application of a cotton ball near the anal opening may absorb small amounts of fecal leakage. Prolapsing hemorrhoids may be treated with band ligation or surgical hemorrhoidectomy. Control of flatus and seepage may be improved by Kegel perineal exercises. Conditions such as ulcerative proctitis that cause tenesmus and urgency, chronic diarrheal conditions, and IBS may result in difficulty in maintaining complete continence, especially if a toilet is not readily available.

Loperamide may be helpful to reduce urge incontinence in patients with loose stools and may be taken in anticipation of situations in which a toilet may not be readily available. Older patients may require more time or assistance to reach a toilet, which may lead to incontinence. Scheduled toileting and the availability of a bedside commode are helpful. Older adult patients with chronic constipation may develop stool impaction leading to "overflow" incontinence.

Major Incontinence

Complete uncontrolled loss of stool reflects a significant problem with central perception or neuromuscular function. Incontinence that occurs without awareness suggests a loss of central awareness (eg, dementia, cerebrovascular accident, multiple sclerosis) or peripheral nerve injury (eg, spinal cord injury, cauda equina syndrome, pudendal nerve damage due to obstetric trauma or pelvic floor prolapse, aging, or diabetes mellitus). Incontinence that occurs despite awareness and active efforts to retain stool suggests sphincteric damage, which may be caused by traumatic childbirth (especially forceps delivery), episiotomy, prolapse, prior anal surgery, and physical trauma.

Physical examination should include careful inspection of the perianal area for hemorrhoids, rectal prolapse, fissures, fistulas, and either gaping or a keyhole defect of the anal sphincter (indicating severe sphincteric injury or neurologic disorder). The perianal skin should be stimulated to confirm an intact anocutaneous reflex. Digital examination during relaxation gives valuable information about resting tone (due mainly to the internal sphincter) and contraction of the external sphincter and pelvic floor during squeezing. It also excludes fecal impaction. Anoscopy is required to evaluate for hemorrhoids, fissures, and fistulas. Proctosigmoidoscopy is useful to exclude rectal carcinoma or proctitis. Anal ultrasonography or pelvic MRI is the most reliable test for definition of anatomic defects in the external and internal anal sphincters. Anal manometry may also be useful to define the severity of weakness, to assess sensation, and to predict response to biofeedback training.

Patients who are incontinent only of loose or liquid stools are treated with bulking agents and antidiarrheal drugs (eg, loperamide, 2 mg before meals and prophylactically before social engagements, shopping trips, etc). Patients with incontinence of solid stool benefit from scheduled toilet use after glycerin suppositories or tap water enemas. Biofeedback training with pelvic floor strengthening (Kegel) exercises (alternating 5-second squeeze and 10-second rest for 10 minutes twice daily) may be helpful in motivated patients to lower the threshold for awareness of rectal filling, strengthen the pelvic floor, and improve continence. In a 2019 randomized controlled trial, global incontinence symptom improvement occurred in 38% of patients instructed on daily pelvic floor contraction exercises (three sets of 10 contractions sustained for up to 10 seconds and two sets of 3 contractions sustained for up to 30 seconds) compared with 18% who did not perform these exercises. Operative management is seldom needed but should be considered in patients with major incontinence due to prior injury to the anal sphincter who have not responded to medical therapy.

When to Refer

- Conservative measures fail.
- Anorectal tests are deemed necessary (manometry, ultrasonography, electromyography).
- A surgically correctable lesion is suspected.

Mazor Y et al. Factors associated with response to anorectal biofeedback therapy in patients with fecal incontinence. Clin Gastroenterol Hepatol. 2021;19:492. [PMID: 32251788]
Pasricha T et al. Fecal incontinence in the elderly. Clin Geriatr Med. 2021;37:71. [PMID: 33213775]
Sbeit W et al. Diagnostic approach to faecal incontinence: what test and when to perform? World J Gastroenterol. 2021;27:1553. [PMID: 33958842]
Whitehead WE et al. Fecal incontinence diagnosed by Rome IV criteria in the United States, Canada, and the United Kingdom. Clin Gastroenterol Hepatol. 2020;18:385. [PMID: 31154029]

OTHER ANAL CONDITIONS

Anal Fissures

Anal fissures are linear or rocket-shaped ulcers that are usually less than 5 mm in length. Most fissures are believed to arise from trauma to the anal canal during defecation, perhaps caused by straining, constipation, or high internal sphincter tone. They occur most commonly in the posterior midline, but 10% occur anteriorly. Fissures that occur off the midline should raise suspicion for Crohn disease, HIV/AIDS, tuberculosis, syphilis, or anal carcinoma. Patients complain of severe, tearing pain during defecation followed by throbbing discomfort that may lead to constipation due to fear of recurrent pain. There may be mild associated hematochezia, with blood on the stool or toilet paper. Anal fissures are confirmed by visual inspection of the anal verge while gently separating the buttocks. Acute fissures look like cracks in the epithelium. Chronic fissures result in fibrosis and the development of a skin tag at the outermost edge (sentinel pile). Digital and anoscopic examinations may cause severe pain and may not be possible. Medical management is directed at promoting effortless, painless bowel movements. Fiber supplements and sitz baths should be prescribed. Topical anesthetics (5% lidocaine; 2.5% lidocaine plus 2.5% prilocaine) may provide temporary relief. Healing occurs within 2 months in up to 45% of patients with conservative management. Chronic fissures may be treated with topical 0.125–0.4% nitroglycerin, diltiazem 2% ointment, or nifedipine 0.5% (1 cm of ointment) applied 2–3 times daily just inside the anus with the tip of a finger for 4–8 weeks, or injection of botulinum toxin (20 units) into the internal anal sphincter. All these treatments result in healing in 60–90% of patients with chronic anal fissure, but headaches occur in up to 40% of patients treated with nitroglycerin. Botulinum toxin may cause transient anal incontinence. Fissures recur in up to

40% of patients after treatment. Chronic or recurrent fissures benefit from lateral internal sphincterotomy; however, minor incontinence may complicate this procedure.

Kyriakakis R et al. What predicts successful nonoperative management with botulinum toxin for anal fissure? Am J Surg. 2020;219:442. [PMID: 31679653]
Lu Y et al. Diagnosis and treatment of anal fissures in 2021. JAMA. 2021;325:688. [PMID: 33591336]
Wald A et al. ACG clinical guidelines: management of benign anorectal disorders. Am J Gastroenterol. 2021;116:1987. [PMID: 34618700]

Perianal Abscess & Fistula

The anal glands located at the base of the anal crypts at the dentate line may become infected, leading to abscess formation. Other causes of abscess include anal fissure and Crohn disease. Abscesses may extend upward or downward through the intersphincteric plane. Symptoms of perianal abscess are throbbing, continuous perianal pain. Erythema, fluctuance, and swelling may be found in the perianal region on external examination or in the ischiorectal fossa on digital rectal examination. Perianal abscesses are treated with local incision and drainage, while ischiorectal abscesses require drainage in the operating room. After drainage of an abscess, most patients are found to have a fistula in ano.

Fistula in ano most often arises in an anal crypt and is usually preceded by an anal abscess. In patients with fistulas that connect to the rectum, other disorders such as Crohn disease, lymphogranuloma venereum, rectal tuberculosis, and cancer should be considered. Fistulas are associated with purulent discharge that may lead to itching, tenderness, and pain. The treatment of Crohn-related fistula is discussed elsewhere in this chapter. Treatment of simple idiopathic fistula in ano is by surgical incision or excision under anesthesia. Care must be taken to preserve the anal sphincters. Surgical fistulotomy for treatment of complex (high, transphincteric) anal fissures carries a high risk of incontinence. Techniques for healing the fistula while preserving the sphincter include an endoanal advancement flap over the internal opening and insertion of a bioprosthetic plug into the fistula opening.

Amato A et al. Evaluation and management of perianal abscess and anal fistula: SICCR position statement. Tech Coloproctol. 2020;24:127. [PMID: 31974827]
Cooper CR et al. Perianal fistulas. Dis Colon Rectum. 2020; 63:129. [PMID: 31914108]
Wasmann KA et al. Treatment of perianal fistulas in Crohn's disease, seton versus anti-TNF versus surgical closure following anti-TNF [PISA]: a randomised controlled trial. J Crohns Colitis. 2020;14:1049. [PMID: 31919501]

Perianal Pruritus

Perianal pruritus is characterized by perianal itching and discomfort. It may be caused by poor anal hygiene associated with fistulas, fissures, prolapsed hemorrhoids, skin tags, and minor incontinence. Conversely, overzealous cleansing with soaps may contribute to local irritation or contact dermatitis. Contact dermatitis, atopic dermatitis, bacterial infections (*Staphylococcus* or *Streptococcus*), parasites (pinworms, scabies), candidal infection (especially in diabetics), sexually transmitted disease (condylomata acuminata, herpes, syphilis, molluscum contagiosum), and other skin conditions (psoriasis, Paget disease, lichen sclerosis) must be excluded. In patients with idiopathic perianal pruritus, examination may reveal erythema, excoriations, or lichenified, eczematous skin. Education is vital to successful therapy. Spicy foods, coffee, chocolate, and tomatoes may cause irritation and should be eliminated. After bowel movements, the perianal area should be cleansed with nonscented wipes premoistened with lanolin followed by gentle drying. A piece of cotton ball should be tucked next to the anal opening to absorb perspiration or fecal seepage. Anal ointments and lotions may exacerbate the condition and should be avoided. A short course of high-potency topical corticosteroid may be tried, although efficacy has not been demonstrated. Diluted capsaicin cream (0.006%) led to symptomatic relief in 75% of patients in a double-blind crossover study.

Cohee MW et al. Benign anorectal conditions: evaluation and management. Am Fam Physician. 2020;101:24. [PMID: 31894930]
Ortega AE et al. Idiopathic pruritus ani and acute perianal dermatitis. Clin Colon Rectal Surg. 2019;32:327. [PMID: 31507341]

16 Liver, Biliary Tract, & Pancreas Disorders

Lawrence S. Friedman, MD

JAUNDICE & EVALUATION OF ABNORMAL LIVER BIOCHEMICAL TESTS

ESSENTIALS OF DIAGNOSIS

- Jaundice results from accumulation of bilirubin in body tissues; the cause may be hepatic or nonhepatic.
- Hyperbilirubinemia may be due to abnormalities in the formation, transport, metabolism, or excretion of bilirubin.
- Persistent mild elevations of the aminotransferase levels are common in clinical practice and caused most often by nonalcoholic fatty liver disease (NAFLD).
- Evaluation of obstructive jaundice begins with ultrasonography and is usually followed by cholangiography.

General Considerations

Jaundice (icterus) results from the accumulation of bilirubin—a product of heme metabolism—in body tissues. Hyperbilirubinemia may be due to abnormalities in the formation, transport, metabolism, or excretion of bilirubin. Total serum bilirubin is normally 0.2–1.2 mg/dL (3.42–20.52 mcmol/L). Mean levels are higher in men than women, higher in White persons and Latinx persons than Black persons and correlate with an increased risk of symptomatic gallstone disease and inversely with the risk of stroke, respiratory disease, CVD, and mortality. Jaundice may not be recognizable until serum bilirubin levels are about 3 mg/dL (51.3 mcmol/L).

Jaundice may be caused by predominantly unconjugated or conjugated bilirubin in the serum (Table 16–1). Unconjugated hyperbilirubinemia may result from overproduction of bilirubin because of hemolysis; impaired hepatic uptake of bilirubin due to certain drugs; or impaired conjugation of bilirubin by glucuronide, as in Gilbert syndrome due to mild decreases in uridine diphosphate (UDP) glucuronyl transferase, or Crigler-Najjar syndrome caused by moderate decreases (type II) or absence (type I) of UDP glucuronyl transferase. Hemolysis alone rarely elevates the serum bilirubin level to more than 7 mg/dL (119.7 mcmol/L). Predominantly conjugated hyperbilirubinemia may result from impaired excretion of bilirubin from the liver due to hepatocellular disease, drugs, sepsis, or hereditary hepatocanalicular transport defects (such as Dubin-Johnson syndrome, progressive familial intrahepatic cholestasis syndromes, and intrahepatic cholestasis of pregnancy) or from extrahepatic biliary obstruction. Features of some hyperbilirubinemic syndromes are summarized in Table 16–2.

Clinical Findings

A. Unconjugated Hyperbilirubinemia

Stool and urine color are normal, and there is mild jaundice and indirect (unconjugated) hyperbilirubinemia with no bilirubin in the urine. Splenomegaly occurs in all hemolytic disorders except in sickle cell disease.

B. Conjugated Hyperbilirubinemia

Conjugated hyperbilirubinemia is often accompanied by pruritus, light-colored stools, and jaundice, although the patient may be asymptomatic. Malaise, anorexia, low-grade fever, and right upper quadrant discomfort are frequent with hepatocellular disease. Dark urine, jaundice, and, in women, amenorrhea occur. An enlarged tender liver, spider telangiectasias, palmar erythema, ascites, gynecomastia, sparse body hair, fetor hepaticus, and asterixis may be present, depending on the cause, severity, and chronicity of liver dysfunction.

C. Biliary Obstruction

There may be right upper quadrant pain, weight loss (suggesting carcinoma), jaundice, pruritus, dark urine, and light-colored stools. Symptoms and signs may be intermittent if caused by a stone, carcinoma of the ampulla, or cholangiocarcinoma. Pain may be absent early in pancreatic cancer. Occult blood in the stools suggests cancer of the ampulla. A palpable gallbladder (Courvoisier sign) is

Table 16–1. Classification of jaundice.

Type of Hyperbilirubinemia	Location and Cause
Unconjugated hyperbilirubinemia (predominantly indirect bilirubin)	Increased bilirubin production (eg, hemolytic anemias, hemolytic reactions, hematoma, pulmonary infarction) Impaired bilirubin uptake and storage (eg, posthepatitis hyperbilirubinemia, Gilbert syndrome, Crigler-Najjar syndrome, drug reactions)
Conjugated hyperbilirubinemia (predominantly direct bilirubin)	**Hereditary Cholestatic Syndromes** (see also Table 16–2)
	Faulty excretion of bilirubin conjugates (eg, Dubin-Johnson syndrome, Rotor syndrome) or pathogenic variant in genes coding for bile salt transport proteins (eg, progressive familial intrahepatic cholestasis syndromes, benign recurrent intrahepatic cholestasis, and some cases of intrahepatic cholestasis of pregnancy)
	Hepatocellular Dysfunction
	Biliary epithelial and hepatocyte damage (eg, hepatitis, hepatic cirrhosis) Intrahepatic cholestasis (eg, certain drugs, biliary cirrhosis, sepsis, postoperative jaundice) Hepatocellular damage or intrahepatic cholestasis resulting from miscellaneous causes (eg, spirochetal infections, infectious mononucleosis, cholangitis, sarcoidosis, lymphomas, hyperthyroidism, industrial toxins)
	Biliary Obstruction
	Choledocholithiasis, biliary atresia, carcinoma of biliary duct, sclerosing cholangitis, IgG_4-related cholangitis, ischemic cholangiopathy, COVID cholangiopathy, choledochal cyst, external pressure on bile duct, pancreatitis, pancreatic neoplasms

Ig, immunoglobulin.

characteristic, but neither specific nor sensitive, of a pancreatic head tumor. Fever and chills are more common in benign obstruction with associated cholangitis.

Diagnostic Studies

(See Tables 16–3 and 16–4.)

A. Laboratory Findings

Elevated serum alanine and AST (ALT and AST) levels reflect hepatocellular injury. Normal reference values for ALT and AST are lower than generally reported when persons with risk factors for fatty liver are excluded. The upper limit of normal for ALT is 29–33 U/L in men and 19–25 U/L in women. Levels decrease with age and correlate with BMI and mortality from liver disease and inversely with caffeine consumption and physical activity. Levels are mildly elevated in more than 25% of persons with untreated celiac disease and in type 1 diabetic patients with so-called glycogenic hepatopathy and often rise transiently in healthy persons who begin taking 4 g of acetaminophen per day or experience rapid weight gain on a fast-food diet. Levels may rise strikingly but transiently in patients with acute biliary obstruction from choledocholithiasis. NAFLD is by far the most common cause of persistent mildly to moderately elevated aminotransferase levels. Elevated ALT and AST levels, often greater than 1000 U/L (20 mckat/L), are the hallmark of hepatocellular necrosis or inflammation. Modest elevations are frequent in systemic infections, including COVID-19. The differential diagnosis of any liver test elevation always includes toxicity caused by drugs, herbal and dietary supplements, and toxins.

Elevated alkaline phosphatase levels are seen in cholestasis or infiltrative liver disease (such as tumor, granulomatous disease, or amyloidosis). Isolated alkaline phosphatase elevations of hepatic rather than bone, intestinal, or placental origin are confirmed by concomitant elevation of gamma-glutamyl transpeptidase or 5′-nucleotidase levels.

B. Imaging

Demonstration of dilated bile ducts by ultrasonography or CT indicates biliary obstruction (90–95% sensitivity). Ultrasonography, CT, and MRI may also demonstrate hepatomegaly, intrahepatic tumors, and portal hypertension. MRI is the most accurate technique for identifying isolated liver lesions such as hemangiomas, focal nodular hyperplasia, or focal fatty infiltration and for detecting hepatic iron overload. The most sensitive techniques for detection of individual small hepatic metastases in patients eligible for resection are multiphasic helical or multislice CT; MRI with use of gadolinium or ferumoxides as contrast agents; CT arterial portography, in which imaging follows intravenous contrast infusion via a catheter placed in the superior mesenteric artery; and intraoperative ultrasonography. Because of its much lower cost, ultrasonography is preferable to CT (~six times more expensive) or MRI (~seven times more expensive) as a screening test for hepatocellular carcinoma in persons with cirrhosis. PET can be used to detect small pancreatic tumors and metastases. Ultrasonography can detect gallstones with a sensitivity of 95%.

Magnetic resonance cholangiopancreatography (MRCP) is a sensitive, noninvasive method of detecting bile duct stones, strictures, and dilatation; however, it is less reliable than endoscopic retrograde cholangiopancreatography (ERCP) for distinguishing malignant from benign strictures. ERCP requires a skilled endoscopist and may be used to demonstrate pancreatic or ampullary causes of jaundice, carry out sphincterotomy and stone extraction, insert a stent

Table 16–2. Hyperbilirubinemic disorders.

	Nature of Defect	Type of Hyperbilirubinemia	Clinical and Pathologic Characteristics
Gilbert syndrome[1]	Reduced activity of uridine diphosphate glucuronyl transferase	Unconjugated (indirect) bilirubin	Benign, asymptomatic hereditary jaundice. Hyperbilirubinemia increased by 24- to 36-hour fast. No treatment required. Associated with reduced mortality from CVD.
Dubin-Johnson syndrome[2]	Reduced excretory function of hepatocytes	Conjugated (direct) bilirubin	Benign, asymptomatic hereditary jaundice. Gallbladder does not visualize on oral cholecystography. Liver darkly pigmented on gross examination. Biopsy shows centrilobular brown pigment. Prognosis excellent.
Rotor syndrome[3]	Reduced hepatic reuptake of bilirubin conjugates	Conjugated (direct) bilirubin	Similar to Dubin-Johnson syndrome, but the liver is not pigmented, and the gallbladder is visualized on oral cholecystography. Prognosis excellent.
Recurrent or progressive intrahepatic cholestasis[4]	Cholestasis, often on a familial basis	Predominantly conjugated (direct) bilirubin	Episodic attacks of or progressive jaundice, itching, and malaise. Onset in early life and may persist for a lifetime. Alkaline phosphatase increased. Cholestasis found on liver biopsy. (Biopsy may be normal during remission.) Prognosis is generally excellent for "benign" recurrent intrahepatic cholestasis but may not be for familial forms.
Intrahepatic cholestasis of pregnancy[5]	Cholestasis	Predominantly conjugated (direct) bilirubin	Benign cholestatic jaundice, usually occurring in the third trimester of pregnancy. Itching, GI symptoms, abnormal liver excretory function tests, and elevated serum bile acid levels (> 10 mcmol/L). Cholestasis noted on liver biopsy. Prognosis excellent, but recurrence with subsequent pregnancies or use of oral contraceptives is characteristic.

[1]Gilbert syndrome generally results from the addition of extra dinucleotide(s) TA sequences to the TATA promoter of the conjugating enzyme *UGT1A1*.
[2]Dubin-Johnson syndrome is caused by a pathogenic variant in the *ABCC2* gene coding for organic anion transporter multidrug resistance protein 2 in bile canaliculi on chromosome 10q24.
[3]Rotor syndrome is caused by pathogenic variants in the genes coding for organic anion transporting polypeptides OATP1B1 and OATP1B3 on chromosome 12p.
[4]Pathogenic variants in genes that control hepatocellular transport systems that are involved in the formation of bile and inherited as autosomal recessive traits are on chromosomes 18q21–22, 2q24, 7q21, and others in families with progressive familial intrahepatic cholestasis. Pathogenic variants of genes on chromosome 18q21–22 alter a P-type ATPase expressed in the small intestine and liver and those on chromosome 2q24 alter the bile acid export pump and also cause benign recurrent intrahepatic cholestasis. Pathogenic variants in the *ABCB4* gene on chromosome 7 that encodes multidrug resistance protein 3 account for progressive familial intrahepatic cholestasis type 3. Less common causes of progressive familial intrahepatic cholestasis are pathogenic variants in genes that encode TJP2, FXR, MY05B, and others.
[5]Pathogenic variants in genes (especially *ABCB4* and *ABCB11*) that encode biliary canalicular transporters account for many cases of intrahepatic cholestasis of pregnancy.

Table 16–3. Liver biochemical tests: normal values and changes in hepatocellular and obstructive jaundice.

Tests	Normal Values	Hepatocellular Jaundice	Obstructive Jaundice
Bilirubin[1] Direct Indirect	 0.1–0.3 mg/dL (1.71–5.13 mcmol/L) 0.2–0.7 mg/dL (3.42–11.97 mcmol/L)	 Increased Increased	 Increased Increased
Urine bilirubin	None	Increased	Increased
Serum albumin	3.5–5.5 g/dL (35–55 g/L)	Decreased	Generally unchanged
Alkaline phosphatase	30–115 U/L (0.6–2.3 mkat/L)	Mildly increased (+)	Markedly increased (++++)
Prothrombin time	INR of 1.0–1.4. After vitamin K, 10% decrease in 24 hours	Prolonged if damage is severe; does not respond to parenteral vitamin K	Prolonged if obstruction is marked; generally responds to parenteral vitamin K
ALT, AST	ALT, ≤ 30 U/L (0.6 mkat/L) (men), ≤ 19 U/L (0.38 mkat/L) (women); AST, 5–40 U/L (0.1–0.8 mkat/L)	Increased, as in viral hepatitis	Minimally increased

[1]Measured by the van den Bergh reaction, which overestimates direct bilirubin in normal persons.

Table 16–4. Causes of serum aminotransferase elevations.[1]

Mild Elevations (< 5 × normal)	Severe Elevations (> 15 × normal)
Hepatic: ALT-predominant	Acute viral hepatitis (A–E, herpes)
Chronic hepatitis B, C, and D	Medications/toxins
Acute viral hepatitis (A-E, EBV, CMV, others)	Ischemic hepatitis
Steatosis/steatohepatitis	Autoimmune hepatitis
Hemochromatosis	Wilson disease
Medications/toxins	Acute bile duct obstruction
Autoimmune hepatitis	Acute Budd-Chiari syndrome
Alpha-1-antitrypsin (alpha-1-antiprotease) deficiency	Hepatic artery ligation
Wilson disease	
Celiac disease	
Glycogenic hepatopathy	
Hepatic: AST-predominant	
Alcohol-related liver injury (AST:ALT > 2:1)	
Cirrhosis	
COVID-19	
Nonhepatic	
Strenuous exercise	
Hemolysis	
Myopathy	
Thyroid disease	
Macro-AST	

[1]Almost any liver disease can cause moderate aminotransferase elevations (5–15 × normal).
CMV, cytomegalovirus; EBV, Epstein-Barr virus.
Reproduced with permission from Green RM et al. AGA technical review on the evaluation of liver chemistry tests. *Gastroenterology*. 2002;123(4):1367–1384.

through an obstructing lesion, or facilitate direct cholangiopancreatoscopy. Complications of ERCP include pancreatitis (5% or less) and, less commonly, cholangitis, bleeding, or duodenal perforation after sphincterotomy. Percutaneous transhepatic cholangiography is an alternative approach to evaluating the anatomy of the biliary tract. Serious complications of PTC occur in 3% and include fever, bacteremia, bile peritonitis, and intraperitoneal hemorrhage. Endoscopic ultrasonography (EUS) is the most sensitive test for detecting small lesions of the ampulla or pancreatic head and for detecting portal vein invasion by pancreatic cancer. It is also accurate for detecting or excluding bile duct stones.

C. Liver Biopsy

Percutaneous liver biopsy is considered the definitive study for determining the cause and histologic severity of hepatocellular dysfunction or infiltrative liver disease, although it is subject to sampling error. It is generally performed under ultrasound or, in some patients with suspected metastatic disease or a hepatic mass, CT guidance. A transjugular route can be used in patients with coagulopathy or ascites, and in selected cases endoscopic ultrasound-guided liver biopsy has proved advantageous. The risk of bleeding after a percutaneous liver biopsy is approximately 0.6% and is increased in persons with a platelet count of 50,000/mcL (50×10^9/L) or less. The risk of death is less than 0.1%. Panels of blood tests (eg, FibroSure, NAFLD fibrosis score, enhanced liver fibrosis score) and, more accurately, ultrasound (vibration-controlled transient elastography, a point-of-care technique), point-shear wave, or bidimensional shear wave (integrated in ultrasound devices), or magnetic resonance elastography to measure liver stiffness are used for estimating the stage of liver fibrosis and degree of portal hypertension without the need for liver biopsy; they are most useful for excluding advanced fibrosis.

When to Refer

Patients with jaundice should be referred for diagnostic procedures.

When to Admit

Patients with liver failure should be hospitalized.

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DISEASES OF THE LIVER

See Chapter 39 for Hepatocellular Carcinoma.

ACUTE HEPATITIS A

ESSENTIALS OF DIAGNOSIS

- Prodrome of anorexia, nausea, vomiting, malaise, aversion to smoking.
- Fever, enlarged and tender liver, jaundice.
- Normal to low white cell count; markedly elevated aminotransferases.

General Considerations

Hepatitis can be caused by viruses, including the five hepatotropic viruses—A, B, C, D, and E—and many drugs and toxic agents; the clinical manifestations may be similar regardless of cause. Hepatitis A virus (HAV) is a 27-nm RNA hepatovirus (in the picornavirus family) that causes

epidemics or sporadic cases of hepatitis. HAV infection is hyperendemic in developing countries. Globally, over 1.5 million people are infected with HAV annually. The virus is transmitted by the fecal-oral route by either person-to-person contact or ingestion of contaminated food or water, and its spread is favored by crowding and poor sanitation. Since introduction of the HAV vaccine in the United States in 1995, the incidence rate of HAV infection has declined from as much as 14 to 0.4 per 100,000 population, with a corresponding decline in the mortality rate from 0.1 to 0.02 death per 100,000 population and an increase in the mean age of infection and death. Nevertheless, over 80% of persons aged 20–60 years in the United States are still susceptible to HAV, and vulnerable populations are especially at risk. The highest incidence rate (2.1 per 100,000) is in adults aged 30–39. Common source outbreaks resulting from contaminated food, including inadequately cooked shellfish, or untreated ground water from wells continue to occur, although no drinking water–associated outbreaks have occurred in the United States since 2009. In 2017, an outbreak beginning in California and extending to at least 33 other states affected a large number of homeless persons and resulted in many deaths. Outbreaks also occur among people who inject drugs or unvaccinated residents in institutions and among men who have sex with men and international adoptees and their contacts. In the United States, international travel emerged as an important risk factor, accounting for over 40% of cases in the early 2000s but a lower percentage in the 2010s. Overall, however, reports of HAV infection increased by nearly 300% during 2016–2018 compared to 2013–2015.

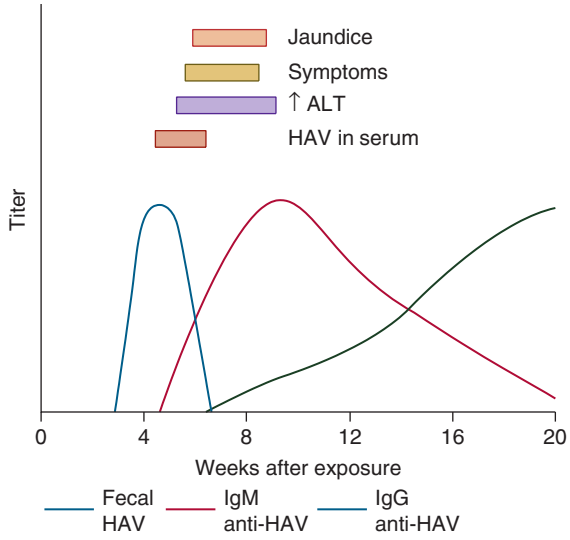
The incubation period averages 30 days. HAV is excreted in feces for up to 2 weeks before clinical illness but rarely after the first week of illness. The mortality rate for hepatitis A is low, and acute liver failure due to hepatitis A is uncommon except for rare instances in which it occurs in a patient with concomitant chronic hepatitis C. There is no chronic carrier state. In the United States, about 30% of the population have serologic evidence of previous HAV infection.

Clinical Findings

A. Symptoms and Signs

Figure 16–1 shows the typical course of acute hepatitis A. Clinical illness is more severe in adults than in children, in whom it is usually asymptomatic. The onset may be abrupt or insidious, with malaise, myalgia, arthralgia, easy fatigability, upper respiratory symptoms, and anorexia. A distaste for smoking, paralleling anorexia, may occur early. Nausea and vomiting are frequent, and diarrhea or constipation may occur. Fever is generally present but is low-grade except in occasional cases in which systemic toxicity may occur. Defervescence and a fall in pulse rate often coincide with the onset of jaundice.

Abdominal pain is usually mild and constant in the right upper quadrant or epigastrium, often aggravated by jarring or exertion, and rarely may be severe enough to simulate cholecystitis. Jaundice occurs after 5–10 days but may appear at the same time as the initial symptoms. In many patients, jaundice never develops. With the onset of jaundice, prodromal symptoms often worsen, followed by



▲ **Figure 16–1.** The typical course of acute type A hepatitis. (Anti-HAV, antibody to hepatitis A virus; HAV, hepatitis A virus.) (Reproduced with permission from Koff RS. Acute viral hepatitis. In: Friedman LS, Keeffe EB. *Handbook of Liver Disease*, 4th ed. Philadelphia: Saunders Elsevier, 2018.)

progressive clinical improvement. Stools may be acholic during this phase. Hepatomegaly—rarely marked—is present in over half of cases. Liver tenderness is usually present. Splenomegaly is reported in 15% of patients, and soft, enlarged lymph nodes—especially in the cervical or epitrochlear areas—may be noted.

The acute illness usually subsides over 2–3 weeks with complete clinical and laboratory recovery by 9 weeks. In some cases, clinical, biochemical, and serologic recovery may be followed by one or two relapses, but recovery is the rule. Acute cholecystitis occasionally complicates the course of acute hepatitis A. Other occasional extrahepatic complications include AKI, arthritis, vasculitis, acute pancreatitis, aplastic anemia, and a variety of neurologic manifestations.

B. Laboratory Findings

The WBC count is normal to low, especially in the preicteric phase. Large atypical lymphocytes may occasionally be seen. Mild proteinuria is common, and bilirubinuria often precedes the appearance of jaundice. Strikingly elevated ALT or AST levels occur early, followed by elevations of bilirubin and alkaline phosphatase; in a minority of patients, the latter persist after aminotransferase levels have normalized. Cholestasis is occasionally marked. Antibody to hepatitis A (anti-HAV) appears early in the course of the illness (Figure 16–1). Both IgM and IgG anti-HAV are detectable in serum soon after the onset. Peak titers of IgM anti-HAV occur during the first week of clinical disease and usually disappear within 3–6 months. Detection of IgM anti-HAV is an excellent test for diagnosing acute hepatitis A. Titers of IgG anti-HAV rise after 1 month of the disease and may persist for years. IgG anti-HAV (in the

absence of IgM anti-HAV) indicates previous exposure to HAV, noninfectivity, and immunity.

Differential Diagnosis

The differential diagnosis includes other viruses that cause hepatitis, particularly hepatitis B (HBV) and C (HCV) viruses, and diseases such as infectious mononucleosis, cytomegalovirus infection, herpes simplex virus infection, Middle East respiratory syndrome, and infections caused by many other viruses, including influenza, Ebola virus, and SARS-CoV-2; spirochetal diseases such as leptospirosis and secondary syphilis; brucellosis; rickettsial diseases such as Q fever; drug-induced liver injury; and ischemic hepatitis (shock liver). Occasionally, autoimmune hepatitis may have an acute onset mimicking acute viral hepatitis. Rarely, metastatic cancer of the liver, lymphoma, or leukemia may present as a hepatitis-like picture.

The prodromal phase of viral hepatitis must be distinguished from other infectious disease such as influenza and COVID-19, upper respiratory infections, and the prodromal stages of the exanthematous diseases. Cholestasis may mimic obstructive jaundice.

Prevention

Strict isolation of patients is not necessary, but hand washing after bowel movements is required. Unvaccinated persons who are exposed to HAV are advised to receive postexposure prophylaxis with a single dose of HAV vaccine or immune globulin (0.01 mL/kg), or both, within 2 weeks of exposure. The vaccine is preferred in healthy persons aged 1 year to 40 years, whereas immune globulin plus the vaccine is preferred in those who are younger than 1 year or older than 40 years, are immunocompromised, or have chronic liver disease.

Vaccination with one of two effective inactivated hepatitis A vaccines available in the United States provides long-term immunity and is recommended for persons living in or traveling to endemic areas (including military personnel), persons over age 40, patients with chronic liver disease upon diagnosis after prescreening for immunity, men who have sex with men, persons with HIV infection, animal handlers, persons who use injection or noninjection drugs, persons experiencing homelessness, persons who are incarcerated, close personal contacts of international adoptees, persons living in group settings for those with developmental disabilities, and persons who request protection against HAV. For healthy travelers, a single dose of vaccine at any time before departure can provide adequate protection. Routine vaccination is advised by the Advisory Committee on Immunization Practices of the CDC for all children aged 12–23 months in the United States, with catch-up vaccination for children and adolescents aged 2–18 years who have not previously received the HAV vaccine. HAV vaccine is also effective in the prevention of secondary spread to household contacts of primary cases. The recommended dose for adults is 1 mL (1440 ELISA units) of Havrix (GlaxoSmithKline) or 1 mL (50 units) of Vaqta (Merck) intramuscularly, followed by a booster dose at 6–18 months. A combined hepatitis A and B vaccine (Twinrix, GlaxoSmithKline) is available.

Treatment

Bed rest is recommended only if symptoms are marked. If nausea and vomiting are pronounced or if oral intake is substantially decreased, intravenous 10% glucose is indicated.

Dietary management consists of palatable meals as tolerated, without overfeeding; breakfast is usually tolerated best. Strenuous physical exertion, alcohol, and hepatotoxic agents should be avoided. Small doses of oxazepam are safe because metabolism is not hepatic; morphine sulfate should be avoided. Corticosteroids have no benefit in patients with viral hepatitis, including those with acute liver failure.

Prognosis

In most patients, clinical recovery is generally complete within 3 months. Laboratory evidence of liver dysfunction may persist for a longer period, but most patients recover completely. Hepatitis A does not cause chronic liver disease, although it may persist for up to 1 year, and clinical and biochemical relapses may occur before full recovery. The mortality rate is less than 1.0%, with a higher rate in older adults than in younger persons.

When to Admit

- Encephalopathy is present.
- INR greater than 1.6.
- The patient is unable to maintain hydration.

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ACUTE HEPATITIS B

ESSENTIALS OF DIAGNOSIS

- Prodrome of anorexia, nausea, vomiting, malaise, aversion to smoking.
- Fever, enlarged and tender liver, jaundice.
- Normal to low WBC count; markedly elevated aminotransferases early in the course.
- Liver biopsy shows hepatocellular necrosis and mononuclear infiltrate but is rarely indicated.

General Considerations

Hepatitis B virus (HBV) is a 42-nm hepadnavirus with a partially double-stranded DNA genome, inner core protein (hepatitis B core antigen, HBcAg), and outer surface coat (hepatitis B surface antigen, HBsAg). There are 10 different genotypes (A–J). HBV is usually transmitted by inoculation of infected blood or blood products or by sexual contact, and it is present in saliva, semen, and vaginal secretions. HBsAg-positive mothers may transmit HBV at delivery.

Since 1990, the incidence of HBV infection in the United States has decreased from 8.5 to 1.5 cases per 100,000 population. The prevalence is 0.27% in persons aged 6 or older. Because of universal vaccination since 1992, exposure to HBV is low among persons aged 18 or younger. HBV is prevalent in men who have sex with men and in people who inject drugs (about 7% of HIV-infected persons are coinfected with HBV), but the greatest number of cases result from heterosexual transmission. Other groups at risk include patients and staff at hemodialysis centers, physicians, dentists, nurses, and personnel working in clinical and pathology laboratories and blood banks. Half of all patients with acute hepatitis B in the United States have previously been incarcerated or treated for a sexually transmitted disease. The risk of HBV infection from a blood transfusion in the United States is no higher than 1 in 350,000 units transfused. Screening for HBV infection is recommended for high-risk groups by the USPSTF.

The incubation period of hepatitis B is 6 weeks to 6 months (average 12–14 weeks). The onset of hepatitis B is more insidious, and the aminotransferase levels are higher on average, than in HAV infection. Acute liver failure occurs in less than 1%, with a mortality rate of up to 60%. Following acute hepatitis B, HBV infection persists in 1–2% of immunocompetent adults, but in a higher percentage of children and immunocompromised adults. There are an estimated 2.4 million persons (including an estimated 1.47 million foreign-born persons from endemic areas) with chronic hepatitis B in the United States and 248 million worldwide. Compared with the general population, the prevalence of chronic HBV infection is increased two- to threefold in non-Latinx Black persons and tenfold in Asian persons. Persons with chronic hepatitis B, particularly when HBV infection is acquired early in life and viral replication persists, are at substantial risk for cirrhosis and hepatocellular carcinoma (up to 25–40%); men are at greater risk than women.

Clinical Findings

A. Symptoms and Signs

The clinical picture of viral hepatitis is extremely variable, ranging from asymptomatic infection without jaundice to acute liver failure and death in a few days to weeks. Figure 16–2 shows the typical course of acute HBV infection. The onset may be abrupt or insidious, and the clinical features are similar to those for acute hepatitis A. Serum sickness may be seen early in acute hepatitis B. Fever is generally present and is low-grade. Defervescence and a fall in pulse rate often coincide with the onset of jaundice. Infection caused by HBV may be associated with glomerulonephritis and polyarteritis nodosa.

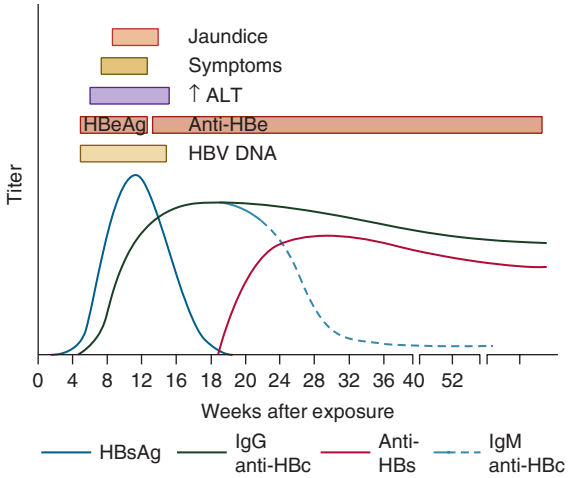


Figure 16–2. The typical course of acute type B hepatitis. Anti-HBe, antibody to HBeAg; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to HBsAg; HBeAg, hepatitis Be antigen; HBsAg, hepatitis B surface antigen. (Reproduced with permission from Koff RS. Acute viral hepatitis. In: Friedman LS, Keeffe EB. *Handbook of Liver Disease*, 3rd ed. Philadelphia: Saunders Elsevier, 2012.)

The acute illness usually subsides over 2–3 weeks with complete clinical and laboratory recovery by 16 weeks. In 5–10% of cases, the course may be more protracted, but less than 1% will develop acute liver failure. Hepatitis B may become chronic.

B. Laboratory Findings

The laboratory features are similar to those for acute hepatitis A, although serum aminotransferase levels are higher on average in acute hepatitis B, and marked cholestasis is not a feature. Marked prolongation of the prothrombin time in severe hepatitis correlates with increased mortality.

There are several antigens and antibodies as well as HBV DNA that relate to HBV infection and that are useful in diagnosis. Interpretation of common serologic patterns is shown in Table 16–5.

1. HBsAg—The appearance of HBsAg in serum is the first evidence of infection, appearing before biochemical evidence of liver disease, and persisting throughout the clinical illness. Persistence of HBsAg more than 6 months after the acute illness signifies chronic hepatitis B.

2. Anti-HBs—Specific antibody to HBsAg (anti-HBs) appears in most individuals after clearance of HBsAg and after successful vaccination against hepatitis B. Disappearance of HBsAg and the appearance of anti-HBs signal recovery from HBV infection, noninfectivity, and immunity.

Table 16–5. Common serologic patterns in hepatitis B virus (HBV) infection and their interpretation.

HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	Interpretation
+	–	IgM	+	–	Acute hepatitis B
+	–	IgG[1]	+	–	Chronic hepatitis B with active viral replication
+	–	IgG	–	+	Inactive HBV carrier state (low HBV DNA level) or HBeAg-negative chronic hepatitis B with active viral replication (high HBV DNA level)
+	+	IgG	+ or –	+ or –	Chronic hepatitis B with heterotypic anti-HBs (about 10% of cases)
–	–	IgM	+ or –	–	Acute hepatitis B
–	+	IgG	–	+ or –	Recovery from hepatitis B (immunity)
–	+	–	–	–	Vaccination (immunity)
–	–	IgG	–	–	False-positive; less commonly, infection in remote past

[1]Low levels of IgM anti-HBc may also be detected.

3. Anti-HBc—IgM anti-HBc appears shortly after HBsAg is detected. In the setting of acute hepatitis, IgM anti-HBc indicates a diagnosis of acute hepatitis B, and it fills the serologic gap in rare patients who have cleared HBsAg but do not yet have detectable anti-HBs. IgM anti-HBc can persist for 3–6 months, and sometimes longer. IgM anti-HBc may also reappear during flares of previously inactive chronic hepatitis B. IgG anti-HBc also appears during acute hepatitis B but persists indefinitely, whether the patient recovers (with the appearance of anti-HBs in serum) or chronic hepatitis B develops (with persistence of HBsAg). In asymptomatic persons such as blood donors, an isolated anti-HBc with no other positive HBV serologic results may represent a falsely positive result or latent infection in which HBV DNA is detectable in serum only by PCR testing.

4. HBeAg—HBeAg is a secretory form of HBcAg that appears in serum during the incubation period shortly after the detection of HBsAg. HBeAg indicates viral replication and infectivity. Persistence of HBeAg beyond 3 months indicates an increased likelihood of chronic hepatitis B. Its disappearance is often followed by the appearance of anti-HBe, generally signifying diminished viral replication and decreased infectivity.

5. HBV DNA—The presence of HBV DNA in serum generally parallels the presence of HBeAg, although HBV DNA is a more sensitive and precise marker of viral replication and infectivity. In some patients with chronic hepatitis B, HBV DNA is present at high levels without HBeAg in serum because of development of a pathogenic variant in the core promoter or pre-core region of the gene that codes HBcAg; these variants prevent synthesis of HBeAg in infected hepatocytes. When additional variants in the core gene are also present, the severity of HBV infection is enhanced and the risk of cirrhosis is increased.

Differential Diagnosis

The differential diagnosis includes hepatitis A and the same disorders listed for the differential diagnosis of acute hepatitis A. In addition, coinfection with hepatitis D virus (HDV) must be considered.

Prevention

Strict isolation of patients is not necessary. Thorough hand washing by medical staff who may contact contaminated utensils, bedding, or clothing is essential. Medical staff should handle disposable needles carefully and not recap them. Screening of donated blood for HBsAg, anti-HBc, and anti-HCV has reduced the risk of transfusion-associated hepatitis markedly. All pregnant women should undergo testing for HBsAg. HBV-infected persons should practice safe sex. Immunoprophylaxis of the neonate reduces the risk of perinatal transmission of HBV infection; when the mother's serum HBV DNA level is 200,000 IU/mL or higher (or the mother's serum HBsAg level is above 4–4.5 $\log_{10}$ IU/mL), antiviral treatment of the mother should also be initiated in the third trimester (see Chronic Hepatitis B & Chronic Hepatitis D). HBV-infected health care workers are not precluded from practicing medicine or dentistry if they follow CDC guidelines.

Hepatitis B immune globulin (HBIG) may be protective—or may attenuate the severity of illness—if given within 7 days after exposure (adult dose is 0.06 mL/kg body weight) followed by initiation of the HBV vaccine series. This approach is recommended for unvaccinated persons exposed to HBsAg-contaminated material via mucous membranes or through breaks in the skin and for individuals who have had sexual contact with a person with HBV infection (irrespective of the presence or absence of HBeAg in the source). HBIG is also indicated for newborn infants of HBsAg-positive mothers, with initiation of the vaccine series at the same time, both within 12 hours of birth (administered at different injection sites).

The CDC recommends HBV vaccination of all infants and children in the United States and all adults who are at risk for hepatitis B (including persons under age 60 with diabetes mellitus) or who request vaccination. Over 90% of recipients of the vaccine mount protective antibody to hepatitis B; immunocompromised persons, including patients receiving dialysis (especially those with diabetes mellitus), respond poorly (see Table 30–7). The standard regimen for adults is 10–20 mcg (depending on the formulation) repeated again at 1 and 6 months, but alternative

schedules have been approved, including accelerated schedules of 0, 1, 2, and 12 months and of 0, 7, and 21 days plus 12 months. For greatest reliability of absorption, the deltoid muscle is the preferred site of inoculation. A newer vaccine, Heplisav-B, which uses a novel immune system–stimulating ingredient, was approved by the FDA for adults in 2017. Immunization requires only two injections, and Heplisav-B appears to be more effective than previous HBV vaccines. When documentation of seroconversion is considered desirable, postimmunization anti-HBs titers may be checked. Protection appears to be excellent even if the titer wanes—persisting for at least 20 years—and booster reimmunization is not routinely recommended but is advised for immunocompromised persons in whom anti-HBs titers fall below 10 mIU/mL. For vaccine nonresponders, three additional vaccine doses may elicit seroprotective anti-HBs levels in 30–50% of persons. Doubling of the standard dose or use of Heplisav-B may also be effective. Universal vaccination of neonates in countries endemic for HBV has reduced the incidence of hepatocellular carcinoma. Incomplete immunization is the most important predictor of liver disease among vaccinees. Unfortunately, approximately 64 million high-risk adults in the United States remain susceptible to HBV.

Treatment

Treatment of acute hepatitis B is the same as that for acute hepatitis A. Encephalopathy or severe coagulopathy indicates acute liver failure, and hospitalization at a liver transplant center is mandatory. Antiviral therapy is generally unnecessary in patients with acute hepatitis B but is usually prescribed in cases of acute liver failure caused by HBV as well as in spontaneous reactivation of chronic hepatitis B presenting as acute-on-chronic liver failure (see Acute Liver Failure).

Prognosis

In most patients, clinical recovery is complete in 3–6 months. Laboratory evidence of liver dysfunction may persist for a longer period, but most patients recover completely. The mortality rate for acute hepatitis B is 0.1–1% but is higher with superimposed hepatitis D.

Chronic hepatitis, characterized by elevated aminotransferase levels for more than 3–6 months, develops in 1–2% of immunocompetent adults with acute hepatitis B, but in as many as 90% of infected neonates and infants and a substantial proportion of immunocompromised adults. Ultimately, cirrhosis develops in up to 40% of those with chronic hepatitis B; the risk of cirrhosis is even higher in HBV-infected patients coinfected with HCV or HIV. Patients with cirrhosis are at risk for hepatocellular carcinoma at a rate of 3–5% per year. Even in the absence of cirrhosis, patients with chronic hepatitis B—particularly those with active viral replication—are at increased risk for hepatocellular carcinoma.

When to Refer

Refer patients with acute hepatitis who require liver biopsy for diagnosis.

When to Admit

- Encephalopathy is present.
- INR greater than 1.6.
- The patient is unable to maintain hydration.

Hwang JP et al. USPSTF 2020 Hepatitis B Screening Recommendation: evidence to broaden screening and strengthen linkage to care. JAMA. 2020;324:2380. [PMID: 33320206]
Sfeir MM et al. Serologic testing for hepatitis B. JAMA. 2021;326:2423. [PMID: 34797375]
US Preventive Services Task Force; Krist AH et al. Screening for hepatitis B virus infection in adolescents and adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2020;324:2415. [PMID: 33320230]
Wong RJ et al. An updated assessment of chronic hepatitis B prevalence among foreign-born persons living in the United States. Hepatology. 2021;74:607. [PMID: 33655536]

ACUTE HEPATITIS C & OTHER CAUSES OF ACUTE VIRAL HEPATITIS

Viruses other than HAV and HBV that can cause hepatitis are hepatitis C virus (HCV), HDV, and hepatitis E virus (HEV) (an enterically transmitted hepatitis seen in epidemic form in Asia, the Middle East, and North Africa and sporadically in Western countries). Human pegivirus (formerly hepatitis G virus [HGV]) rarely, if ever, causes frank hepatitis. In immunocompromised and rare immunocompetent persons, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus should be considered in the differential diagnosis of hepatitis. Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), SARS coronavirus infection (SARS-CoV-2), Ebola virus infection, and influenza may be associated with elevated serum aminotransferase levels (occasionally marked). Unidentified pathogens account for a small percentage of cases of acute viral hepatitis.

1. Hepatitis C

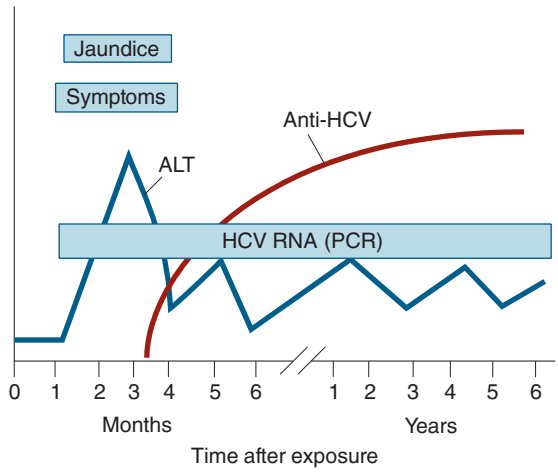
HCV is a single-stranded RNA virus (hepacivirus) with properties similar to those of flaviviruses. Seven major genotypes of HCV have been identified. In the past, HCV was responsible for over 90% of cases of posttransfusion hepatitis, yet only 4% of cases of hepatitis C were attributable to blood transfusions. Over 60% of cases are transmitted by injection drug use, and both reinfection and superinfection of HCV are common in people who actively inject drugs. Body piercing, tattoos, and hemodialysis are risk factors. The risk of sexual and maternal–neonatal transmission is low and may be greatest in a subset of patients with high circulating levels of HCV RNA. Having multiple sexual partners may increase the risk of HCV infection, and HIV coinfection, unprotected receptive anal intercourse with ejaculation, and sex while high on methamphetamine increase the risk of HCV transmission in men who have sex with men. Transmission via breastfeeding has not been documented. An outbreak of hepatitis C in patients with immune deficiencies has occurred in some recipients of intravenous immune globulin. Hospital- and outpatient facility–acquired transmission has occurred via

multidose vials of saline used to flush Portacaths; through reuse of disposable syringes; through drug "diversion" and tampering with injectable opioids by an infected health care worker; through contamination of shared saline, radiopharmaceutical, and sclerosant vials; via inadequately disinfected endoscopy equipment; and between hospitalized patients on a liver unit. In the developing world, unsafe medical practices lead to a substantial number of cases of HCV infection. Incarceration in prison is a risk factor, with a seroprevalence of 26% in the United States and rates as high as 90% in some states. In many patients, the source of infection is unknown. Coinfection with HCV is found in at least 30% of HIV-infected persons. HIV infection leads to an increased risk of acute liver failure and more rapid progression of chronic hepatitis C to cirrhosis; in addition, HCV increases the hepatotoxicity of antiretroviral therapy. The number of cases of chronic HCV infections in the United States is reported to have decreased from 3.2 million in 2001 to 2.3 million in 2013 with a small increase to 2.4 million between 2013 and 2016, although estimates of at least 4.6 million exposed and 3.5 million infected have also been reported. The incidence of new cases of acute, symptomatic hepatitis C declined from 1992 to 2005, but after 2002 an increase was observed in persons aged 15 to 24, because of injection drug use, and since 2010 there has been a 3.8-fold increase in its overall incidence. An increase has also been observed in women of reproductive age. Worldwide, 71 million people are infected with HCV, with the highest rates in central and east Asia, north Africa, and the Middle East.

Clinical Findings

A. Symptoms and Signs

Figure 16–3 shows the typical course of HCV infection. The incubation period for hepatitis C averages 6–7 weeks, and clinical illness is often mild, usually asymptomatic, and characterized by waxing and waning aminotransferase elevations and a high rate (greater than 80%) of chronic hepatitis. In pregnant patients with chronic hepatitis C, serum aminotransferase levels frequently normalize despite persistence of viremia, only to increase again after delivery.



▲ **Figure 16–3.** The typical course of acute and chronic hepatitis C. Anti-HCV, antibody to hepatitis C virus by enzyme immunoassay; HCV RNA PCR, hepatitis C viral RNA by PCR.

B. Laboratory Findings

Diagnosis of hepatitis C is based on an enzyme immunoassay (EIA) that detects antibodies to HCV. Anti-HCV is not protective, and in patients with acute or chronic hepatitis, its presence in serum generally signifies that HCV is the cause. A diagnosis of hepatitis C may be confirmed by using an assay for HCV RNA. Occasional persons are found to have anti-HCV without HCV RNA in the serum, suggesting recovery from HCV infection in the past.

Complications

HCV is a pathogenic factor in mixed cryoglobulinemia and membranoproliferative glomerulonephritis and may be related to lichen planus, autoimmune thyroiditis, lymphocytic sialadenitis, idiopathic pulmonary fibrosis, sporadic porphyria cutanea tarda, monoclonal gammopathies, CVD, and type 2 diabetes mellitus. HCV infection confers a 20–30% or more increased risk of B-cell non-Hodgkin (predominantly marginal zone) lymphoma, and chronic HCV infection (especially genotype 1) is associated with an increased risk of end-stage renal disease. Hepatic steatosis is a particular feature of infection with HCV genotype 3 and may also occur in patients infected with other HCV genotypes who have risk factors for fatty liver. HCV infection during pregnancy is associated with preterm birth and intrahepatic cholestasis of pregnancy.

Prevention

Testing donated blood for HCV has helped reduce the risk of transfusion-associated hepatitis C from 10% in 1990 to about one case per two million units in 2011. The USPSTF recommends that asymptomatic adults aged 18–79 be screened for HCV infection. The CDC recommends HCV screening for all persons over age 18 at least once in a lifetime and all pregnant women (in both cases except in settings where the prevalence of HCV infection is less than 0.1% [very rare]). HCV-infected persons should practice safe sex, but there is little evidence that HCV is spread easily by sexual contact or perinatally, and no specific preventive measures are recommended for infected persons in a monogamous relationship or for infected pregnant women. Because most cases of HCV infection are acquired by injection drug use, public health officials have recommended avoidance of shared needles and creation of needle exchange programs for injection drug users. As yet, there is no vaccine for HCV. Vaccination against HAV (after prescreening for prior immunity) and HBV is recommended for patients with chronic hepatitis C.

Treatment

A 6-week course of ledipasvir and sofosbuvir has been shown to prevent chronic hepatitis in patients with acute genotype-1 hepatitis C and lack of spontaneous clearance

after 3 months (see Chronic Viral Hepatitis). Treatment of acute hepatitis C may be cost effective and is particularly recommended in people who inject drugs.

Prognosis

In most patients, clinical recovery is complete in 3–6 months. Laboratory evidence of liver dysfunction may persist for a longer period. The overall mortality rate is less than 1%, but the rate is reportedly higher in older people and has declined since 2013. Acute liver failure due to HCV is rare in the United States.

Chronic hepatitis, which progresses slowly in many cases, develops in as many as 85% of all persons with acute hepatitis C. Ultimately, cirrhosis develops in up to 30% of those with chronic hepatitis C; the risk of cirrhosis and hepatic decompensation is higher in patients coinfected with both HCV and HBV or HIV. Patients with cirrhosis are at risk for hepatocellular carcinoma at a rate of 3–5% per year. Long-term morbidity and mortality in patients with chronic hepatitis C is lower in Black than in White patients and lowest in those infected with HCV genotype 2 and highest in those with HCV genotype 3.

Cacoub P et al. Extrahepatic manifestations of chronic HCV infection. N Engl J Med. 2021;384:1038. [PMID: 33730456]
Jin F et al. Prevalence and incidence of hepatitis C virus infection in men who have sex with men: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021;6:39. [PMID: 33217341]
Kushner T et al. Changing epidemiology, implications, and recommendations for hepatitis C in women of childbearing age and during pregnancy. J Hepatol. 2021;74:734. [PMID: 33248169]
Schillie S et al. CDC recommendations for hepatitis C screening among adults—United States, 2020. MMWR Recomm Rep. 2020;69:1. [PMID: 32271723]

2. Hepatitis D

HDV is a defective RNA virus that causes hepatitis only in association with HBV infection and specifically only in the presence of HBsAg; it is cleared when the latter is cleared.

HDV may coinfect with HBV or may superinfect a person with chronic hepatitis B, usually by percutaneous exposure. When acute hepatitis D is coincident with acute HBV infection, the infection is generally similar in severity to acute hepatitis B alone. In chronic hepatitis B, superinfection by HDV appears to carry a worse short-term prognosis, often resulting in acute liver failure or severe chronic hepatitis that progresses rapidly to cirrhosis.

New cases of hepatitis D are infrequent in the United States primarily because of the control of HBV infection, and cases seen today are usually from cohorts infected years ago who survived the initial impact of hepatitis D and now have cirrhosis. These patients are at risk for decompensation and have a threefold increased risk of hepatocellular carcinoma. HDV is estimated to cause 18% of cases of cirrhosis and 20% of cases of hepatocellular carcinoma associated with HBV infection. New cases are seen primarily in immigrants from endemic areas, including Africa, central Asia, Eastern Europe, and the Amazon region of Brazil. As many as 13% of HBV carriers are infected with HDV worldwide; principal risk factors are injecting drug use, high-risk sexual behavior, and HIV and HCV coinfections. The diagnosis of hepatitis D is made by detection of antibody to hepatitis D antigen (anti-HDV) and, where available, hepatitis D antigen (HDAg) or HDV RNA in serum.

Rizzetto M et al. The changing context of hepatitis D. J Hepatol. 2021;74:1200. [PMID: 33484770]

3. Hepatitis E

HEV is a 27- to 34-nm RNA hepevirus (in the Hepeviridae family) that is a major cause of acute hepatitis throughout Central and Southeast Asia (about 16% of the population there have antibodies to the virus), and it should be considered in patients with acute hepatitis after a trip to an endemic area. In rare cases, hepatitis E can be mistaken for drug-induced liver injury. In industrialized countries, it may be spread by swine, and having a pet in the home and consuming undercooked organ meats or infected cow's milk are risk factors. The risk appears to be increased in patients undergoing hemodialysis.

Illness generally is self-limited (no carrier state), but instances of chronic hepatitis with rapid progression to cirrhosis attributed to HEV genotype 3 have been reported in transplant recipients (particularly when tacrolimus rather than cyclosporine is used as the main immunosuppressant) and, rarely, in persons with HIV infection, preexisting liver disease, or cancer undergoing chemotherapy. The diagnosis of acute hepatitis E is made most readily by testing for IgM anti-HEV in serum, although available tests may not be reliable.

Reported extrahepatic manifestations include arthritis; pancreatitis; thyroiditis; myocarditis; glomerulonephritis; monoclonal gammopathy; thrombocytopenia; aplastic anemia; a variety of neurologic complications, including Guillain-Barré syndrome and neuralgic amyotrophy (which involves the brachial plexuses bilaterally); and hemophagocytic lymphohistiocytosis. In endemic regions, the mortality rate is high (15–25%) in pregnant women. The risk of hepatic decompensation and death is increased in patients with underlying chronic liver disease.

A 3-month course of treatment with oral ribavirin has been reported to induce sustained clearance of HEV RNA from the serum in 78% of patients with persistent HEV infection and may be considered in patients with severe acute hepatitis E. Improved public hygiene reduces the risk of HEV infection in endemic areas. Recombinant vaccines against HEV have shown promise in clinical trials, and one (Hecolin) is approved in China.

ACUTE LIVER FAILURE

ESSENTIALS OF DIAGNOSIS

- May be fulminant or subfulminant; both forms carry a poor prognosis.
- Acetaminophen and idiosyncratic drug reactions are the most common causes.

General Considerations

Acute liver failure may be fulminant or subfulminant. Fulminant hepatic failure is characterized by the development of hepatic encephalopathy within 8 weeks after the onset of acute liver injury. Coagulopathy (INR 1.5 or higher) is invariably present. Subfulminant hepatic failure occurs when these findings appear between 8 weeks and 6 months after the onset of acute liver injury and carries an equally poor prognosis. Acute-on-chronic liver failure refers to acute deterioration in liver function (often caused by infection) and associated failure of other organs in a person with preexisting chronic liver disease.

An estimated 1600 cases of acute liver failure occur each year in the United States. Toxicity caused by acetaminophen (a direct hepatotoxin) is the most common cause, accounting for at least 45% of cases. Suicide attempts account for 44% of cases of acetaminophen-induced hepatic failure, and unintentional overdoses ("therapeutic misadventures"), which are often a result of a decrease in the threshold toxic dose because of chronic alcohol use or fasting and have been reported after weight loss surgery, account for at least 48%. Other causes include idiosyncratic (in some cases, immune-mediated) drug reactions (the second most common cause, with antibiotics, antituberculosis drugs, and antiepileptics implicated most commonly), viral hepatitis, poisonous mushrooms (*Amanita phalloides*), shock, heat stroke, Budd-Chiari syndrome, malignancy (most commonly lymphomas), Wilson disease, Reye syndrome, fatty liver of pregnancy and other disorders of fatty acid oxidation, autoimmune hepatitis, parvovirus B19 infection, and rarely grand mal seizures. The cause is indeterminate in approximately 5.5% of cases. The risk of acute liver failure is increased in patients with diabetes mellitus, and outcome is worsened by obesity. Herbal and dietary supplements are thought to be contributory to acute liver failure in a substantial portion of cases, regardless of cause, and may be associated with lower rates of transplant-free survival. Acute-on-chronic liver failure is often precipitated by a bacterial infection or an alcohol binge and alcohol-associated hepatitis.

Viral hepatitis accounts for only 12% of all cases of acute liver failure. The decline of viral hepatitis as the principal cause of acute liver failure is due in part to universal vaccination of infants and children against hepatitis B and the availability of the hepatitis A vaccine. Acute liver failure may occur after reactivation of hepatitis B in carriers who receive immunosuppressive therapy. In endemic areas, hepatitis E is an important cause of acute liver failure, particularly in pregnant women. Hepatitis C is a rare cause of acute liver failure in the United States, but acute hepatitis A or B superimposed on chronic hepatitis C may cause acute liver failure.

Clinical Findings

GI symptoms, systemic inflammatory response, and kidney dysfunction are common. Clinically significant bleeding is uncommon and reflects severe systemic inflammation rather than coagulopathy. Adrenal insufficiency and subclinical myocardial injury (manifesting as an elevated serum troponin I level) often complicate acute liver failure. Jaundice may be absent or minimal early in the course, but laboratory tests show severe hepatocellular damage. In acetaminophen toxicity, serum aminotransferase elevations are often towering (greater than 5000 U/L), and acetaminophen is undetectable in plasma in 50% of cases. In acute liver failure due to microvesicular steatosis (eg, fatty liver of pregnancy), serum aminotransferase elevations may be modest (less than 300 U/L). Over 10% of patients have an elevated serum amylase level at least three times the upper limit of normal, often because of renal dysfunction. The blood ammonia level is typically elevated and correlates (along with the Model for End-Stage Liver Disease [MELD] score) with the development of encephalopathy and intracranial hypertension. Intracranial hypertension rarely develops when the blood ammonia level is less than 75 mcmol/L and is invariable when it is greater than 200 mcmol/L. The severity of extrahepatic organ dysfunction (as assessed by the Sequential Organ Failure Assessment [SOFA]) also correlates with the likelihood of intracranial hypertension. AKI frequently complicates acute-on-chronic liver failure.

Treatment

The treatment of acute liver failure is directed toward achieving metabolic and hemodynamic stability. Intravascular volume should be preserved, but large-volume infusions of hypotonic fluids should be avoided. Norepinephrine is the preferred vasopressor; vasopressin may be added for persistent hypotension. Hypoglycemia should be prevented. Intermittent renal replacement therapy may be required. To preserve muscle mass and immune function, enteral administration of protein, 1–1.5 g/kg/day, is advised, with careful monitoring of the ammonia level.

Cerebral edema and sepsis are the leading causes of death. Prophylactic antibiotic therapy decreases the risk of infection, observed in up to 90%, but has no effect on survival and is not routinely recommended. Microbiological screening cultures should be obtained for patients admitted to hospital. For suspected sepsis, broad coverage is indicated. Despite a high rate of adrenal insufficiency, corticosteroids do not reduce mortality and may lower overall survival in patients with a high MELD score, although they may reduce vasopressor requirements. Stress gastropathy prophylaxis with an H_2-receptor blocker or PPI is recommended. Administration of acetylcysteine (140 mg/kg orally followed by 70 mg/kg orally every 4 hours for an additional 17 doses or 150 mg/kg in 5% dextrose intravenously over 15 minutes followed by 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours) prevents acetaminophen toxicity if administered within 12 hours of ingestion and may be beneficial when given up to 72 hours after ingestion. For massive acetaminophen overdoses, treatment with intravenous acetylcysteine may need to be extended in duration until the serum aminotransferase levels are declining and serum acetaminophen levels are undetectable. Treatment with acetylcysteine improves cerebral blood flow and oxygenation as well as transplant-free survival in patients with stage 1 or 2 encephalopathy due to acute liver failure of any cause. Penicillin G (300,000 to 1 million U/kg/day) or silibinin

(silymarin or milk thistle), which is not licensed in the United States, is administered to patients with mushroom poisoning. Nucleoside analogs are recommended for patients with acute liver failure caused by HBV (see Chronic Viral Hepatitis), and intravenous acyclovir has shown benefit in those with herpes simplex virus hepatitis. Plasmapheresis combined with D-penicillamine has been used in acute liver failure due to Wilson disease. Subclinical seizure activity is common in patients with acute liver failure, but the value of prophylactic phenytoin is uncertain.

Early transfer to a liver transplantation center is essential. The head of the patient's bed should be elevated to 30 degrees, and patients with stage 3 or 4 encephalopathy should be intubated. In some centers, extradural sensors are placed in patients at high risk for intracranial hypertension to monitor intracranial pressure for impending cerebral edema with the goal of maintaining the intracranial pressure below 20 mm Hg and the cerebral perfusion pressure above 70 mm Hg but may be associated with complications. Lactulose is of uncertain value. Mannitol, 0.5 g/kg, or 100–200 mL of a 20% solution by intravenous infusion over 10 minutes, may decrease cerebral edema but should be used with caution in patients with advanced CKD. Intravenously administered hypertonic saline to induce hypernatremia (serum sodium concentration of 145–155 mEq/L [145–155 mmol/L]) also may reduce intracranial hypertension. Hypothermia to a temperature of 32–34°C may reduce intracranial pressure when other measures have failed and may improve survival long enough to permit liver transplantation, although a controlled trial showed no benefit, and some authorities recommend a target core temperature of 35–36°C. The value of hyperventilation is uncertain. A short-acting barbiturate, propofol, or intravenous boluses of indomethacin, 25 mg, are considered for refractory intracranial hypertension. Hemodialysis raises intracranial pressure and should be avoided, but continuous renal replacement therapy may be used, if necessary, in patients with AKI.

Prognosis

With earlier recognition of acute liver failure, the frequency of cerebral edema has declined, and overall survival has improved steadily since the 1970s and is now as high as 75%. However, the survival rate in acute liver failure with severe encephalopathy is as low as 20%. The cause of liver injury is the most important determinant of transplant-free survival. In acetaminophen hepatotoxicity, the transplant-free survival is 75%, and no more than 8% of patients undergo liver transplantation. Survival rates are also favorable for hepatitis A, ischemic hepatitis, and pregnancy-related liver disease. For patients with acute liver failure not due to acetaminophen, the outlook is poor in patients younger than 10 and older than 40 years of age and in those with an idiosyncratic drug reaction but appears to be improved when acetylcysteine is administered to patients with stage 1 or 2 encephalopathy. Other adverse prognostic factors are a serum bilirubin level greater than 18 mg/dL (307.8 mcmol/L), INR higher than 6.5, onset of encephalopathy more than 7 days after the onset of jaundice, and a low factor V level (less than 20% of normal in patients younger than 30 years and 30% or less in those 30 years of age or older). For acetaminophen-induced acute liver failure, indicators of a poor outcome are acidosis (pH < 7.3), INR greater than 6.5, and azotemia (serum creatinine 3.4 mg/dL [283.22 mcmol/L] or higher), whereas a rising serum alpha-fetoprotein level predicts a favorable outcome. Other predictors of poor survival in patients with acute liver failure are an elevated blood lactate level (greater than 3.5 mEq/L [3.5 mmol/L]), elevated blood ammonia level (greater than 211 mcg/dL [124 mcmol/L]), and possibly hyperphosphatemia (greater than 3.7 mg/dL [1.2 mmol/L]). The development of thrombocytopenia in the first week is associated with the development of multiorgan system failure and a poor outcome. A number of prognostic indices have been proposed: the "BiLE" score, based on the serum bilirubin, serum lactate, and etiology; the Acute Liver Failure Early Dynamic (ALFED) model, based on the arterial ammonia level, serum bilirubin, INR, and hepatic encephalopathy; and the Acute Liver Failure Study Group (ALFSG) index, based on coma grade, INR, serum bilirubin and phosphorous levels, and serum levels of M30, a cleavage product of cytokeratin-18 caspase. The likelihood of transplant-free survival on admission has been reported to be predicted by a regression model that incorporates the grade of hepatic encephalopathy, etiology, vasopressor use, and log transformations of the serum bilirubin and INR. For acetaminophen-induced acute liver failure, a model that incorporates hepatic encephalopathy grade equal to or greater than 3, Glasgow coma score, cardiovascular failure, mean arterial pressure, INR, serum bilirubin, serum AST, serum creatinine, arterial pH, and arterial lactate has shown good discrimination. In general, emergency liver transplantation is considered for patients with stage 2 to stage 3 encephalopathy or a MELD score of 30.5 or higher (see Cirrhosis) and is associated with a 70% survival rate at 5 years. For mushroom poisoning, liver transplantation should be considered when the interval between ingestion and the onset of diarrhea is less than 8 hours or the INR is 6.0 or higher, even in the absence of encephalopathy. Acute-on-chronic liver failure has a poor prognosis, particularly when associated with kidney dysfunction; some patients may be candidates for liver transplantation.

When to Admit

All patients with acute liver failure should be hospitalized.

Stravitz RT et al. Acute liver failure. Lancet. 2019;394:869. [PMID: 31498101]

CHRONIC VIRAL HEPATITIS

ESSENTIALS OF DIAGNOSIS

- Defined by chronic infection (HBV, HCV, HDV) for longer than 3–6 months.
- Diagnosis is usually made by antibody tests and viral nucleic acid in serum.

General Considerations

Chronic hepatitis is defined as chronic necroinflammation of the liver of more than 3–6 months' duration, demonstrated by persistently elevated serum aminotransferase levels or characteristic histologic findings, often in the absence of symptoms. In many cases, the diagnosis of chronic hepatitis may be made on initial presentation. The causes of chronic hepatitis include HBV, HCV, and HDV as well as autoimmune hepatitis; alcohol-associated and nonalcoholic steatohepatitis; certain medications, such as isoniazid and nitrofurantoin; Wilson disease; alpha-1-antitrypsin (antiprotease) deficiency; and, rarely, celiac disease. Mortality from chronic HBV and HCV infection has been rising in the United States, and HCV has surpassed HIV as a cause of death. Chronic hepatitis is categorized based on etiology; grade of portal, periportal, and lobular inflammation (minimal, mild, moderate, or severe); and stage of fibrosis (none, mild, moderate, severe, cirrhosis). In the absence of advanced cirrhosis, patients are often asymptomatic or have mild nonspecific symptoms. The World Health Organization has outlined a strategy for eliminating chronic viral hepatitis by 2030 (by vaccinating against hepatitis B, ensuring blood safety and injection safety, timely birth dosing of hepatitis B vaccine, harm reduction from injecting drug use, and testing and treating persons coinfected with hepatitis viruses and HIV).

1. Chronic Hepatitis B & Chronic Hepatitis D

Clinical Findings & Diagnosis

Chronic hepatitis B afflicts 248 million people worldwide (2 billion overall have been infected; endemic areas include Asia and sub-Saharan Africa) and an estimated 2.4 million (predominantly males) in the United States. It may be noted as a continuum of acute hepatitis B or diagnosed because of repeated detection of HBsAg in serum, often with elevated aminotransferase levels.

Five phases of chronic HBV infection are recognized: immune tolerant phase, immune active (or immune clearance) phase, inactive HBsAg carrier state, reactivated chronic hepatitis B phase, and the HBsAg-negative phase. In the immune tolerant phase **(HBeAg-positive chronic HBV infection),** HBeAg and HBV DNA are present in serum and are indicative of active viral replication, and serum aminotransferase levels are normal, with little necroinflammation in the liver. This phase is common in infants and young children whose immature immune system fails to mount an immune response to HBV.

Persons in the immune tolerant phase and those who acquire HBV infection later in life may enter an immune active phase **(HBeAg-positive chronic hepatitis B),** in which aminotransferase and HBV DNA levels are elevated and necroinflammation is present in the liver, with a risk of progression to cirrhosis (at a rate of 2–5.5% per year) and of hepatocellular carcinoma (at a rate of more than 2% per year in those with cirrhosis); low-level IgM anti-HBc is present in serum in about 70%.

Patients enter the inactive HBsAg carrier state **(HBeAg-negative chronic HBV infection)** when biochemical improvement follows immune clearance. This improvement coincides with disappearance of HBeAg and reduced HBV DNA levels (less than 10^5 copies/mL, or less than 20,000 IU/mL) in serum, appearance of anti-HBe, and integration of the HBV genome into the host genome in infected hepatocytes. Patients in this phase are at a low risk for cirrhosis (if it has not already developed) and for hepatocellular carcinoma, and those with persistently normal serum aminotransferase levels infrequently have histologically significant liver disease, especially if the HBsAg level is low.

The reactivated chronic hepatitis B phase **(HBeAg-negative chronic hepatitis B)** may result from infection by a pre-core mutant of HBV or from spontaneous mutation of the pre-core or core promoter region of the HBV genome during the course of chronic hepatitis caused by wild-type HBV. HBeAg-negative chronic hepatitis B accounts for less than 10% of cases of chronic hepatitis B in the United States, up to 50% in southeast Asia, and up to 90% in Mediterranean countries, reflecting in part differences in the frequencies of HBV genotypes. In reactivated chronic hepatitis B, there is a rise in serum HBV DNA levels and possible progression to cirrhosis (at a rate of 8–10% per year), particularly when additional pathogenic variants in the core gene of HBV are present. Risk factors for reactivation include male sex and HBV genotype C as well as immunosuppression. Treatment of HCV infection with direct-acting antiviral agents has been reported to lead to instances of HBV reactivation.

In patients with either HBeAg-positive or HBeAg-negative chronic hepatitis B, the risk of cirrhosis and of hepatocellular carcinoma correlates with the serum HBV DNA level. Other risk factors include advanced age, male sex, alcohol use, cigarette smoking, HBV genotype C, and coinfection with HCV or HDV. HIV coinfection is also associated with an increased frequency of cirrhosis when the CD4 count is low.

Only 1% of treated and untreated patients per year reach the **HBsAg-negative phase,** in which anti-HBe may remain detectable, serum ALT levels are normal, and HBV DNA is undetectable in serum but remains present in the liver. This phase is also referred to as a "functional cure." In some cases, anti-HBs appears in serum.

Acute **hepatitis D** infection superimposed on chronic HBV infection may result in severe chronic hepatitis, which may progress rapidly to cirrhosis and may be fatal. Patients with long-standing chronic hepatitis D and B often have inactive cirrhosis and are at risk for decompensation and hepatocellular carcinoma. The diagnosis is confirmed by detection of anti-HDV or HDAg (or HDV RNA) in serum.

Treatment

Patients with active viral replication (HBeAg and HBV DNA [10^5 copies/mL or more, or 20,000 IU/mL or more] in serum and elevated aminotransferase levels) may be treated with a nucleoside or nucleotide analog or with pegylated interferon. Nucleoside and nucleotide analogs are preferred because they are better tolerated and can be taken orally. For patients who are HBeAg-negative, the

threshold for treatment is a serum HBV DNA level of 10^4 copies/mL, or 2000 IU/mL. If the threshold HBV DNA level for treatment is met but the serum ALT level is normal, treatment may still be considered in patients over age 35–40 if liver biopsy or a noninvasive assessment of liver fibrosis demonstrates a fibrosis stage of 2 of 4 (moderate) or higher. Therapy is aimed at reducing and maintaining the serum HBV DNA level to the lowest possible levels, thereby leading to normalization of the ALT level and histologic improvement. An additional goal in HBeAg-positive patients is seroconversion to anti-HBe, and some responders eventually clear HBsAg. Although nucleoside and nucleotide analogs generally have been discontinued 6–12 months after HBeAg-to-anti-HBe seroconversion, some patients (especially Asian patients) serorevert to HBeAg after discontinuation, have a rise in HBV DNA levels and recurrence of hepatitis activity, and require long-term therapy, which also is required when seroconversion does not occur and in patients with cirrhosis (at least until HBsAg clears and possibly indefinitely). HBeAg-negative patients with chronic hepatitis B also generally require long-term therapy because relapse is frequent when therapy is stopped. The goal of therapy is "functional cure," characterized by loss of HBsAg, with or without appearance of anti-HBs, and undetectable HBV DNA in serum, associated with improved patient outcomes.

The available nucleoside and nucleotide analogs—entecavir, tenofovir, lamivudine, adefovir, and telbivudine—differ in efficacy and rates of resistance; however, in HBeAg-positive patients, they all achieve an HBeAg-to-anti-HBe seroconversion rate of about 20% at 1 year, with higher rates after more prolonged therapy. The preferred first-line oral agents are entecavir and tenofovir. Entecavir is rarely associated with resistance unless a patient is already resistant to lamivudine. The daily dose is 0.5 mg orally for patients not resistant to lamivudine and 1 mg for patients who previously became resistant to lamivudine. Suppression of HBV DNA in serum occurs in nearly all treated patients, and histologic improvement is observed in 70% of patients. Entecavir has been reported to cause lactic acidosis when used in patients with decompensated cirrhosis. Tenofovir disoproxil fumarate, 300 mg orally daily, is equally effective and is used as a first-line agent or when resistance to a nucleoside analog has developed. Like entecavir, tenofovir has a low rate of resistance when used as initial therapy. Long-term use may lead to an elevated serum creatinine level and reduced serum phosphate level (Fanconi-like syndrome) that is reversible with discontinuation of the drug. Tenofovir alafenamide, 25 mg orally daily, is an alternative formulation of tenofovir that is associated with a lower rate of renal and bone toxicity than tenofovir disoproxil fumarate.

Nucleoside and nucleotide analogs are well tolerated even in patients with decompensated cirrhosis (for whom the treatment threshold may be an HBV DNA level less than 10^4 copies/mL and therapy should be continued indefinitely) and may be effective in patients with rapidly progressive hepatitis B ("fibrosing cholestatic hepatitis") following organ transplantation.

Nucleoside analogs are also recommended to prevent reactivation in both inactive HBV carriers and those positive only for anti-HBc prior to the initiation of immunosuppressive therapy (especially B-cell–depleting agents, such as rituximab, and anti-tumor necrosis factor antibody or moderate- or high-dose corticosteroid therapy) or cancer chemotherapy. In patients infected with both HBV and HIV, antiretroviral therapy, including two drugs active against both viruses (eg, tenofovir plus lamivudine or emtricitabine), has been recommended when treatment of HIV infection is indicated. Tenofovir, telbivudine, and lamivudine have been shown to be safe in pregnant women. Antiviral therapy has been recommended, beginning in the third trimester, when the mother's serum HBV DNA level is 200,000 IU/mL or higher to reduce levels at the time of delivery.

Peginterferon alfa-2a is still an alternative to the oral agents in selected cases. A dose of 180 mcg subcutaneously once weekly for 48 weeks leads to sustained normalization of aminotransferase levels, disappearance of HBeAg and HBV DNA from serum, and appearance of anti-HBe in up to 40% of treated patients and results in improved survival. A response is most likely in patients with a low baseline HBV DNA level and high aminotransferase levels and is more likely in those who are infected with HBV genotype A than with other genotypes (especially genotype D). Moreover, many complete responders eventually clear HBsAg and develop anti-HBs in serum. Relapses are uncommon in complete responders who seroconvert from HBeAg to anti-HBe. Peginterferon may be considered to avoid long-term therapy with an oral agent, as in young women who may want to become pregnant in the future. Patients with HBeAg-negative chronic hepatitis B have a response rate of 60% after 48 weeks of therapy with peginterferon, but the response may not be durable once peginterferon is stopped. The response to peginterferon is poor in patients with HIV coinfection.

In **chronic hepatitis D**, peginterferon alfa-2b (1.5 mcg/kg/wk for 48 weeks) may lead to normalization of serum aminotransferase levels, histologic improvement, and elimination of HDV RNA from serum in 20–50% of patients, but relapse may occur, and tolerance is poor. Nucleoside and nucleotide analogs are generally not effective in treating chronic hepatitis D.

Prognosis

The sequelae of chronic hepatitis secondary to hepatitis B include cirrhosis, liver failure, and hepatocellular carcinoma. The 5-year mortality rate is 0–2% in those without cirrhosis, 14–20% in those with compensated cirrhosis, and 70–86% following decompensation. The risk of cirrhosis and hepatocellular carcinoma correlates with serum HBV DNA levels, and a focus of therapy is to suppress HBV DNA levels below 300 copies/mL (60 IU/mL). In patients with cirrhosis, even low levels of HBV DNA in serum increase the risk of hepatocellular carcinoma compared with undetectable levels. HBV genotype C is associated with a higher risk of cirrhosis and hepatocellular carcinoma than other genotypes. Antiviral treatment

improves the prognosis in responders, prevents (or leads to regression of) cirrhosis, and decreases the frequency of liver-related complications (although the risk of hepatocellular carcinoma does not become as low as that in inactive HBV carriers and hepatocellular carcinoma may even occur after clearance of HBsAg). A risk score (PAGE-B) based on a patient's age, sex, and platelet count has been reported to predict the 5-year risk of hepatocellular carcinoma in White patients taking entecavir or tenofovir.

Anderson RT et al. Association between seroclearance of hepatitis B surface antigen and long-term clinical outcomes of patients with chronic hepatitis B virus infection: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2021;19:463. [PMID: 32473348]

Shiffman ML (guest editor). Challenging issues in the management of chronic hepatitis B virus. Clin Liver Dis. 2021;25:673. [Full issue]

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2. Chronic Hepatitis C

Clinical Findings & Diagnosis

Chronic hepatitis C develops in up to 85% of patients with acute hepatitis C. It is clinically indistinguishable from chronic hepatitis due to other causes and may be the most common. Worldwide, 71 million people are infected with HCV, with 1.8% of the US population infected. Peak prevalence in the United States (about 4%) is in persons born between 1945 and 1964. In approximately 40% of cases, serum aminotransferase levels are persistently normal. The diagnosis is confirmed by detection of anti-HCV by EIA. In rare cases of suspected chronic hepatitis C but a negative EIA, HCV RNA is detected by PCR testing. Progression to cirrhosis occurs in 20% of affected patients after 20 years, with an increased risk in men, those who drink more than 50 g of alcohol daily, and those who acquire HCV infection after age 40 years. The rate of fibrosis progression accelerates after age 50. Black persons have a higher rate of chronic hepatitis C but lower rates of fibrosis progression and response to therapy than White persons. Immunosuppressed persons—including patients with hypogammaglobulinemia or HIV infection with a low CD4 count or those receiving immunosuppressants—appear to progress more rapidly to cirrhosis than immunocompetent persons with chronic hepatitis C. Tobacco and cannabis smoking and hepatic steatosis also appear to promote progression of fibrosis, whereas coffee consumption appears to slow progression. Persons with chronic hepatitis C and persistently normal serum aminotransferase levels usually have mild chronic hepatitis with slow or absent progression to cirrhosis; however, cirrhosis is present in 10% of these patients. Serum fibrosis testing (eg, FibroSure) or elastography may be used to identify the absence of fibrosis or presence of cirrhosis.

Treatment

The introduction of direct-acting antiviral agents has rapidly expanded the therapeutic armamentarium against HCV (Table 16–6). With the introduction of all-oral regimens, the criterion for a sustained virologic response was shortened from 24 weeks to 12 weeks following the completion of treatment. The definition of clearance of HCV RNA requires use of a sensitive real-time reverse transcriptase-PCR assay to monitor HCV RNA during treatment (the lower limit of quantification should be 25 IU/mL or less, and the limit of detection should be 10–15 IU/mL).

Several types of direct-acting antiviral agents have been developed (Tables 16–6 and 16–7). HCV protease inhibitors ("…previrs") generally have high antiviral potency but differ with respect to the development of resistance (although resistance-associated substitutions in the HCV genome tend not to persist after therapy with these agents is stopped). Examples include glecaprevir and voxilaprevir. Medications in this class are contraindicated in patients with decompensated cirrhosis.

NS5A inhibitors ("…asvirs"), such as ledipasvir and velpatasvir, are characterized by high antiviral potency at picomolar doses. The cross-genotype efficacy of these agents varies.

HCV polymerase inhibitors ("…buvirs") are categorized as nucleoside or nucleotide analog and non-nucleoside polymerase inhibitors. Nucleos(t)ide analogs are active against all HCV genotypes and have a high barrier to resistance. Sofosbuvir has been the sole available agent in this category. Non-nucleos(t)ide polymerase inhibitors, such as dasabuvir, are the weakest class of compounds against HCV because of a low barrier to resistance. Drugs in this class are generally more active against HCV genotype 1b than HCV genotype 1a. They have been developed to be used only in combination with the other direct-acting antiviral agents, mainly protease inhibitors and NS5A inhibitors.

In late 2019, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America recommended two preferred and highly effective combination regimens: glecaprevir plus pibrentasvir for 8 weeks for genotypes 1–6 and sofosbuvir plus velpatasvir for 12 weeks for genotypes 1, 2, 4, 5, or 6; subsequently sofosbuvir and velpatasvir was approved for genotype 3 (see Table 16–7). The combination of glecaprevir and pibrentasvir is approved for 8 weeks in treatment-naïve, noncirrhotic or compensated cirrhotic and treatment-experienced noncirrhotic patients, including those coinfected with HIV, and for 12 weeks in treatment-experienced, compensated cirrhotic patients. Sofosbuvir and velpatasvir should also be administered for 12 weeks in treatment-experienced compensated cirrhotic patients. Additional modifications may be required in patients with genotype-3 treatment-experienced compensated or decompensated cirrhosis. The combination of glecaprevir and pibrentasvir is also a pangenotypic option for patients with CKD, including those receiving dialysis. The combination of sofosbuvir, velpatasvir, and voxilaprevir is occasionally recommended as "rescue" therapy in patients with nonresponse or relapse following treatment with an NS5A-containing regimen. Where available, testing for resistance-associated substitutions may be helpful in some cases before re-treatment. Use of any regimen containing a protease inhibitor is contraindicated in patients with decompensated cirrhosis.

Table 16–6. Direct-acting antiviral agents for HCV infection (in alphabetical order within class).[1]

Agent	Genotype(s)	Dose[2]	Comment
NS3/4A Protease Inhibitors			
Glecaprevir	1–6	300 mg orally once daily	Used in combination with pibrentasvir[3] with or without ribavirin
Grazoprevir	1 and 4	100 mg orally once daily	Used in combination with elbasvir[4]
Paritaprevir	1 and 4	150 mg orally once daily	Used in combination with ombitasvir and dasabuvir; ritonavir (100 mg) boosted[5]; for genotype 1b with cirrhosis and genotype 1a, used with ribavirin. Used in combination with ombitasvir, ritonavir boosting, and ribavirin for genotype 4[6]
Simeprevir	1 and 4	150 mg orally once daily	Used in combination with sofosbuvir
Voxilaprevir	1–6	100 mg orally once daily	Used in combination with sofosbuvir and velpatasvir[7]
NS5A Inhibitors			
Daclatasvir[8]	1–6	60 mg orally once daily	Used in combination with sofosbuvir (genotypes 1–6, with or without ribavirin depending on presence of cirrhosis) or with asunaprevir (not available in the United States)
Elbasvir	1 and 4	50 mg orally once daily	Used in combination with grazoprevir (see above)
Ledipasvir	1, 4–6	90 mg orally once daily	Used in combination with sofosbuvir[9]
Ombitasvir	1 and 4	25 mg orally once daily	Used in combination with paritaprevir (ritonavir boosted) with or without dasabuvir and with or without ribavirin as per paritaprevir above
Pibrentasvir	1–6	120 mg orally once daily	Used in combination with glecaprevir with or without ribavirin
Velpatasvir	1–6	100 mg orally once daily	Used in combination with sofosbuvir,[10] may be used with sofosbuvir and voxilaprevir
NS5B Nucleos(t)ide Polymerase Inhibitor			
Sofosbuvir	1–6	400 mg orally once daily	Used in combination with ribavirin (genotypes 2 and 3) or with simeprevir (genotypes 1 and 4) or with daclatasvir (all genotypes) or with ledipasvir (genotypes 1, 3, and 4) or with velpatasvir (all genotypes) or with velpatasvir and voxilaprevir (all genotypes)
NS5B Non-Nucleos(t)ide Polymerase Inhibitor			
Dasabuvir	1 and 4	250 mg orally twice daily	Used in combination with paritaprevir (ritonavir boosted) and ombitasvir with or without ribavirin as per paritaprevir above

[1]Regimens approved by the FDA as of early 2022.
[2]The preferred regimen and duration of treatment may vary depending on HCV genotype, presence or absence of cirrhosis or CKD, or nonresponse to prior therapy for HCV infection. In selected cases, testing for resistance-associated substitutions may be considered.
[3]Marketed as Mavyret (AbbVie).
[4]Marketed as Zepatier (Merck) for HCV genotypes 1 and 4 infection.
[5]Marketed as Viekira Pak and Viekira XR (AbbVie).
[6]Marketed as Technivie (AbbVie).
[7]Marketed as Vosevi (Gilead Sciences).
[8]Approved by the FDA for use with sofosbuvir in HCV genotypes 1 and 3 infection but taken off the market in the United States in 2019.
[9]Marketed as Harvoni (Gilead Sciences).
[10]Marketed as Epclusa (Gilead Sciences).

Overall treatment rates are still less than 20% and lowest among Latinx persons and persons with Medicaid or indigent care insurance. The cost of direct-acting antiviral agents has been high (although declining), and lack of insurance coverage has often been a barrier to their use. Additional factors to consider in the selection of a regimen are the presence of cirrhosis or kidney dysfunction, prior treatment, potential drug interactions (of which there are many), and the likelihood that a patient may require liver transplantation in the future. Certain cytochrome P450/P-glycoprotein inducing medications, such as carbamazepine, phenytoin, and phenobarbital, contraindicate the use of all HCV direct-acting antiviral regimens. HCV infection is easy to cure with oral direct-acting agents, with expected sustained virologic response rates well above 90%. Treatment failure is infrequent and most likely in patients infected with HCV genotype 1a or 3, particularly in association with cirrhosis.

Antiviral therapy has been shown to be beneficial in the treatment of cryoglobulinemia associated with chronic hepatitis C; an acute flare of cryoglobulinemia may first require treatment with rituximab, cyclophosphamide plus methylprednisolone, or plasma exchange. As noted above, patients with HCV and HIV coinfection

Table 16–7. Preferred FDA-approved oral direct-acting antiviral (DAA) treatment regimens for HCV infection.[1]

Regimen	Indication	Duration of Treatment in Noncirrhotic Treatment-Naïve Patients (weeks)
Glecaprevir and pibrentasvir	Genotypes 1–6 and DAA-experienced genotype 1	8
Sofosbuvir and velpatasvir	Genotypes 1–6, and DAA-experienced genotypes 1b and 2	12
Sofosbuvir, velpatasvir, and voxilaprevir	DAA-experienced genotypes 1–6	–

[1]Based on the American Association for the Study of Liver Diseases/Infectious Diseases Society of America 2018 Guidance. In late 2019, two preferred regimens were proposed: glecaprevir and pibrentasvir for 8 weeks (genotypes 1–6) and sofosbuvir and velpatasvir for 12 weeks (genotypes 1, 2, 4, 5, 6). See HCV Guidance: Recommendation for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org, accessed December 17, 2021.

have been shown to respond well to treatment of HCV infection. Moreover, in persons coinfected with HCV and HIV, long-term liver disease–related mortality increases as HIV infection–related mortality is reduced by antiretroviral therapy. Occasional instances of reactivation of HBV infection, as well as herpesvirus, have occurred with direct-acting antiviral agents for HCV infection, and all candidates should be prescreened for HBV infection, with the initiation of antiviral prophylactic therapy in those who are HbsAg positive before treatment of HCV infection is begun.

Prognosis

Chronic hepatitis C is an indolent, often subclinical disease that may lead to cirrhosis and hepatocellular carcinoma after decades. The overall mortality rate in patients with transfusion-associated hepatitis C may be no different from that of an age-matched control population. Nevertheless, mortality or transplantation rates clearly rise to 5% per year once cirrhosis develops. A risk score combining age, sex, platelet count, and AST-to-ALT ratio has been proposed. There is some evidence that HCV genotype 1b is associated with a higher risk of hepatocellular carcinoma than other genotypes. Antiviral therapy has a beneficial effect on mortality, cardiovascular events, type 2 diabetes mellitus, and quality of life, is cost effective, appears to retard and even reverse fibrosis, and reduces (but does not eliminate) the risk of decompensated cirrhosis and hepatocellular carcinoma in responders with advanced fibrosis. Even patients who achieve a sustained virologic response remain at an increased risk for mortality compared with the general population. An increased risk of death from extrahepatic cancers has been described in this group, as well as in patients who achieve suppression of HBV infection. Although mortality from cirrhosis and hepatocellular carcinoma due to hepatitis C is still substantial, the need for liver transplantation for chronic hepatitis C has declined, and survival after transplantation has improved. The risk of mortality from drug addiction is higher than that for liver disease in patients with chronic hepatitis C. HCV infection appears to be associated with increased cardiovascular mortality, especially in persons with diabetes mellitus and hypertension. Statin use has been reported to be associated with improved virologic response to antiviral therapy and decreased progression of liver fibrosis and frequency of hepatocellular carcinoma.

When to Refer

- For liver biopsy.
- For antiviral therapy.

When to Admit

For complications of decompensated cirrhosis.

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Sarrazin C. Treatment failure with DAA therapy: importance of resistance. J Hepatol. 2021;74:1472. [PMID: 33716089]

AUTOIMMUNE HEPATITIS

ESSENTIALS OF DIAGNOSIS

- Usually young to middle-aged women.
- Chronic hepatitis with high serum globulins and characteristic liver histology.
- Positive antinuclear antibody (ANA) or smooth muscle antibody, or both, in most cases in the United States.
- Responds to corticosteroids.

General Considerations

Autoimmune hepatitis is usually seen in young women but can occur in either sex at any age. The incidence, which has been rising, and prevalence are estimated to be approximately 2 and 31 per 100,000 population, respectively.

The risk of autoimmune hepatitis is increased in first-degree relatives of affected patients.

Clinical Findings

A. Symptoms and Signs

The onset is usually insidious. About 25% of cases present with acute severe hepatitis (and occasionally acute liver failure), and some cases follow a viral illness (such as hepatitis A, Epstein-Barr infection, or measles) or exposure to a drug or toxin (such as nitrofurantoin, minocycline, hydralazine, methyldopa, infliximab, or an immune checkpoint inhibitor). Exacerbations may occur postpartum. Amenorrhea may be a presenting feature, and the frequency of depression appears to be increased. Thirty-four percent of patients, and particularly older patients, are asymptomatic. Examination may reveal a healthy-appearing young woman with multiple spider telangiectasias, cutaneous striae, acne, hirsutism, and hepatomegaly. Extrahepatic features include arthritis, Sjögren syndrome, thyroiditis, nephritis, ulcerative colitis, and Coombs-positive hemolytic anemia. Patients, especially older patients, with autoimmune hepatitis are at increased risk for cirrhosis, which, in turn, increases the risk of hepatocellular carcinoma (at a rate of about 1% per year).

B. Laboratory Findings

Serum aminotransferase levels may be greater than 1000 U/L, and the total bilirubin is usually increased. Autoimmune hepatitis has been classified as type I or type II, although the clinical features and response to treatment are similar between the two types. In type I (classic) autoimmune hepatitis, ANA or smooth muscle antibodies (either or both) are usually detected in serum. Serum gammaglobulin levels are typically elevated (up to 5–6 g/dL [0.05–0.06 g/L]). In acute severe autoimmune hepatitis, ANA are absent and serum IgG is normal, each in up to 39% of cases. Antibodies to soluble liver antigen (anti-SLA) characterize a variant of type I that is marked by severe disease, a high relapse rate after treatment, and absence of the usual antibodies (ANA and smooth muscle antibodies). Type II, seen more often in girls under age 14 in Europe, is characterized by circulating antibodies to liver-kidney microsome type 1 (anti-LKM1) without smooth muscle antibodies or ANA. In some cases, antibodies to liver cytosol type 1, are detected. Type II autoimmune hepatitis can be seen in patients with autoimmune polyglandular syndrome type 1. Concurrent primary biliary cholangitis (PBC) or primary sclerosing cholangitis ("overlap syndrome") has been recognized in 7–13% and 6–11% of patients with autoimmune hepatitis, respectively. Liver biopsy is indicated to help establish the diagnosis (interface hepatitis is the hallmark), evaluate disease severity and stage of fibrosis, and determine the need for treatment. Histologic features of NAFLD are found in 17–30% of patients with autoimmune hepatitis. Cirrhosis is present in 28–33% of adults at presentation.

Simplified diagnostic criteria based on the detection of autoantibodies (1 point for a titer of greater than 1:40 or 2 points for a titer of greater than 1:80), elevated IgG levels (1 point for IgG level greater than or equal to upper limit of normal or 2 points for level greater than or equal to 1.1 times upper limit of normal), characteristic histologic features (1 or 2 points depending on how typical the features are), and exclusion of viral hepatitis (2 points) can be useful for diagnosis; a total score of 6 indicates probable and a score of 7 indicates definite autoimmune hepatitis with a high degree of specificity but moderate sensitivity. Diagnostic criteria for an overlap of autoimmune hepatitis and PBC ("Paris criteria") have been proposed.

Treatment

Prednisone with or without azathioprine (often started 2 weeks after prednisone) improves symptoms; decreases the serum bilirubin, aminotransferase, and gamma-globulin levels; and reduces hepatic inflammation. Symptomatic patients with aminotransferase levels elevated tenfold (or fivefold if the serum globulins are elevated at least twofold) are optimal candidates for therapy, and asymptomatic patients with modest enzyme elevations may be considered for therapy depending on the clinical circumstances and histologic severity; however, asymptomatic patients usually remain asymptomatic, have either mild hepatitis or inactive cirrhosis on liver biopsy specimens, and have a good long-term prognosis without therapy.

Prednisone is given initially in a dose of 30 mg orally daily with azathioprine, 50 mg orally daily, which is generally well tolerated and permits the use of lower corticosteroid doses than a regimen beginning with prednisone 60 mg orally daily alone. A decrease in serum AST levels by 80% after 8 weeks predicts normalization of AST levels at 1 year. Intravenous corticosteroids or prednisone, 60 mg orally daily, is recommended for patients with acute severe autoimmune hepatitis; azathioprine is often started 2 weeks later. In patients with noncirrhotic autoimmune hepatitis, budesonide, 3 mg orally two or three times daily, may be at least as effective as prednisone as first-line treatment and associated with fewer side effects. Whether patients should undergo testing for the genotype of thiopurine methyltransferase prior to treatment with azathioprine to predict toxicity is debated. Adjusting the dose of azathioprine based on metabolite levels, as in IBD, has been suggested. Blood counts are monitored weekly for the first 2 months of therapy and monthly thereafter because of the small risk of bone marrow suppression. The dosage of prednisone is lowered from 30 mg/day after 1 week to 20 mg/day and again after 2 or 3 weeks to 15 mg/day. Treatment is response-guided, and ultimately, a maintenance dosage of 10 mg/day should be achieved. While symptomatic improvement is often prompt, biochemical improvement is more gradual, with normalization of serum aminotransferase levels after an average of 22 months. Histologic resolution of inflammation lags biochemical remission by 3–6 months and repeat liver biopsy should be considered in persons with at least 2 years of biochemical remission. Failure of aminotransferase levels to return to normal invariably predicts lack of histologic resolution.

The response rate to therapy with prednisone and azathioprine is 80%, with remission in 65% by 3 years. Older patients are more likely to respond than younger patients

and those with, hyperbilirubinemia or a high MELD score (12 or higher, see Cirrhosis). Fibrosis may reverse with therapy and rarely progresses after apparent biochemical and histologic remission. Once complete remission is achieved, therapy may be withdrawn, but the subsequent relapse rate is 90% by 3 years. Relapses may again be treated in the same manner as the initial episode, with the same remission rate. After successful treatment of a relapse, the patient may continue taking azathioprine (up to 2 mg/kg) or the lowest dose of prednisone with or without azathioprine (50 mg/day) needed to maintain aminotransferase levels as close to normal as possible; another attempt at withdrawing therapy may be considered in patients remaining in remission long term (eg, 4 years or longer). During pregnancy, flares can be treated with prednisone, and maintenance azathioprine does not have to be discontinued.

Nonresponders to corticosteroids and azathioprine (failure of serum aminotransferase levels to decrease by 50% after 6 months) may be considered for a trial of cyclosporine, tacrolimus, sirolimus, everolimus, methotrexate, rituximab, or infliximab. Mycophenolate mofetil, 500 mg increased to 1 g twice daily, is an effective alternative to azathioprine in patients who cannot tolerate it but is less effective in nonresponders to azathioprine and is a known teratogen that must be withdrawn prior to conception. It may be effective in up to 60% of patients refractory to or intolerant of corticosteroids. Occasionally, 6-mercaptopurine may be tolerated in patients who do not tolerate azathioprine. Bone density should be monitored—particularly in patients receiving maintenance corticosteroid therapy—and measures undertaken to prevent or treat osteoporosis (see Chapter 26). Liver transplantation may be required for treatment failures and patients with a severe acute presentation (immediately in those with acute liver failure and after 2 weeks in those with acute severe autoimmune hepatitis and a lack of improvement with corticosteroids), but the outcome may be worse than that for PBC because of an increased rate of infectious complications. As immunosuppression is reduced, the disease has been recognized to recur in up to 70% of transplanted livers at 5 years (and rarely to develop de novo); sirolimus can be effective in such cases.

Prognosis

Overall long-term mortality of patients with autoimmune hepatitis and cirrhosis appears to be twofold higher than that of the general population despite response to immunosuppressive therapy. Factors that predict the need for liver transplantation or that predict liver-related death include the following: (1) age 20 years or younger or age 60 years or older at presentation, (2) low serum albumin level at diagnosis, (3) cirrhosis at diagnosis, (4) the presence of anti-SLA, and (5) incomplete normalization of the serum ALT level after 6 months of treatment. The disease appears to be more aggressive in Black patients than in White patients.

When to Refer

- For liver biopsy.
- For immunosuppressive therapy.

When to Admit

- Hepatic encephalopathy.
- INR greater than 1.6.

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Mack CL et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. Hepatology. 2020;72:671. [PMID: 31863477]
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ALCOHOL-ASSOCIATED LIVER DISEASE

ESSENTIALS OF DIAGNOSIS

- Chronic alcohol intake usually exceeds 80 g/day in men and 30–40 g/day in women with alcohol-associated hepatitis or cirrhosis.
- Fatty liver is often asymptomatic.
- Fever, right upper quadrant pain, tender hepatomegaly, and jaundice characterize alcohol-associated hepatitis, but the patient may be asymptomatic.
- AST is usually elevated but infrequently > 300 U/L (6 mckat/L); AST is > ALT, often by a factor of two or more.
- Alcohol-associated hepatitis is often reversible, but it is the most common precursor of cirrhosis in the United States.

General Considerations

Excessive alcohol intake can lead to fatty liver, hepatitis, and cirrhosis. Validated tools, such as the Alcohol Use Disorders Inventory Test (AUDIT), can be used to identify persons with alcohol abuse and dependence (see Table 1–7). Alcohol-associated hepatitis is characterized by acute or chronic inflammation and parenchymal necrosis of the liver induced by alcohol and is often a reversible disease, but it is the most common precursor of cirrhosis in the United States. It is associated with four to five times the number of hospitalizations and deaths as hepatitis C. Mortality from alcohol-associated liver disease has been increasing since 1999.

The frequency of alcohol-associated cirrhosis is estimated to be 10–15% among persons who consume over 50 g of alcohol (4 oz of 100-proof whiskey, 15 oz of wine, or four 12-oz cans of beer) daily for over 10 years (although the risk of cirrhosis may be lower for wine than for a comparable intake of beer or spirits). The risk of cirrhosis is lower (5%) in the absence of other cofactors such as chronic viral hepatitis and obesity. Genetic factors may also

account for differences in susceptibility to and severity of liver disease. Women appear to be more susceptible than men, in part because of lower gastric mucosal alcohol dehydrogenase levels, but young men who drink excessively are at increased risk for liver disease later in life when they are no longer drinking as much.

Clinical Findings

A. Symptoms and Signs

The clinical presentation of alcohol-associated liver disease can vary from asymptomatic hepatomegaly to a rapidly fatal acute illness (acute-on-chronic liver failure) or end-stage cirrhosis. A recent period of heavy drinking, complaints of anorexia and nausea, and the demonstration of hepatomegaly and jaundice strongly suggest the diagnosis. Abdominal pain and tenderness, splenomegaly, ascites, fever, and encephalopathy may be present. Infection, including invasive aspergillosis, is common in patients with severe alcohol-associated hepatitis.

B. Laboratory Findings

In patients with steatosis, mild liver enzyme elevations may be the only laboratory abnormality. Anemia (usually macrocytic) may be present. Leukocytosis with a shift to the left is common in patients with severe alcohol-associated hepatitis. Leukopenia is occasionally seen and resolves after cessation of drinking. About 10% of patients have thrombocytopenia related to a direct toxic effect of alcohol on megakaryocyte production or to hypersplenism.

AST is usually elevated but infrequently above 400 U/L (6 mckat/L). AST is greater than ALT, usually by a factor of two or more. Serum alkaline phosphatase is generally elevated, but seldom more than three times the normal value. Serum bilirubin is increased in 60–90% of patients with alcohol-associated hepatitis.

Serum bilirubin levels greater than 10 mg/dL (171 mcmol/L) and marked prolongation of the prothrombin time (6 seconds or more above control) indicate severe alcohol-associated hepatitis with a mortality rate above 30%. The serum albumin is depressed, and the gamma-globulin level (especially IgA) is elevated in 50–75% of individuals, even in the absence of cirrhosis. Increased transferrin saturation, hepatic iron stores, and sideroblastic anemia are found in many alcoholic patients. Folic acid deficiency may coexist.

C. Imaging

Imaging studies can detect moderate to severe hepatic steatosis reliably but not inflammation or fibrosis. Ultrasonography helps exclude biliary obstruction and identifies subclinical ascites. CT with intravenous contrast or MRI may be indicated in selected cases to evaluate patients for collateral vessels, space-occupying lesions of the liver, or concomitant disease of the pancreas.

D. Liver Biopsy

Liver biopsy, if done, demonstrates macrovesicular fat and, in patients with alcohol-associated hepatitis, polymorphonuclear infiltration with hepatic necrosis, Mallory (or Mallory-Denk) bodies (alcoholic hyaline), and perivenular and perisinusoidal fibrosis. Micronodular cirrhosis may be present as well. The findings are similar to those of nonalcoholic steatohepatitis.

Differential Diagnosis

Alcohol-associated hepatitis may be closely mimicked by cholecystitis and cholelithiasis and by drug toxicity. Other causes of hepatitis or chronic liver disease may be excluded by serologic or biochemical testing, imaging studies, or liver biopsy. A formula based on the AST/ALT ratio, BMI, mean corpuscular volume, and sex has been reported to reliably distinguish alcohol-associated liver disease from NAFLD.

Treatment

A. General Measures

Abstinence from alcohol is essential. Hospitalized patients should be monitored for alcohol withdrawal; the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) is often used in practice (see Figure 25–3). Acamprosate, naltrexone, or baclofen may be considered in combination with counseling to reduce the likelihood of recidivism. Baclofen appears to be safe in persons with advanced alcohol-associated liver disease but can worsen hepatic encephalopathy. Fatty liver is quickly reversible with abstinence. Every effort should be made to provide sufficient amounts of carbohydrates and calories in anorectic patients to reduce endogenous protein catabolism, promote gluconeogenesis, and prevent hypoglycemia. Nutritional support (30–40 [and no less than 21.5] kcal/kg with 1.0–1.5 g/kg as protein) improves liver disease, but not necessarily survival, in patients with malnutrition. Intensive enteral nutrition is difficult to implement, however. The administration of micronutrients, particularly folic acid, thiamine, and zinc, is indicated, especially when deficiencies are noted; glucose administration increases the thiamine requirement and can precipitate Wernicke-Korsakoff syndrome if thiamine is not coadministered. Nephrotoxic drugs should be avoided in patients with severe alcohol-associated hepatitis.

B. Pharmacologic Measures

Methylprednisolone, 32 mg/day orally, or the equivalent, for 1 month, may reduce short-term (1-month but not 6-month) mortality in patients with alcohol-associated hepatitis and encephalopathy, a modified Maddrey discriminant function index (defined by the patient's prothrombin time minus the control prothrombin time times 4.6 plus the total bilirubin in mg/dL) of 32 or more, or a MELD score of 20 or more, particularly those with a MELD score between 25 and 39 (see Cirrhosis). Concomitant GI bleeding or infection may not preclude treatment with corticosteroids if otherwise indicated, but treatment with prednisolone increases the risk of serious infections during and after treatment is completed. The combination of corticosteroids and N-acetylcysteine has been reported to further improve 1-month but not 6-month survival and

reduce the risk of hepatorenal syndrome and infections; the combination may be superior to corticosteroids alone, but more data are needed.

Pentoxifylline, 400 mg orally three times daily for 4 weeks, decreases the risk of hepatorenal syndrome. It does not appear to reduce short-term mortality. Its use is not recommended in some guidelines, but it has been used when corticosteroids are contraindicated. The addition of pentoxifylline to prednisolone does not appear to improve survival but may reduce the frequency of hepatorenal syndrome compared with prednisolone alone.

Prognosis

A. Short-Term

The overall mortality rate for alcohol-associated hepatitis is 34% (20% within 1 month) without corticosteroid therapy. Individuals in whom the prothrombin time prohibits liver biopsy have a 42% mortality rate at 1 year. Other unfavorable prognostic factors are older age, a serum bilirubin greater than 10 mg/dL (171 mcmol/L), hepatic encephalopathy, coagulopathy, azotemia, leukocytosis, sepsis and other infections, systematic inflammatory response syndrome (which is associated with multiorgan failure), lack of response to corticosteroid therapy, a low serum transferrin level, and possibly a paucity of steatosis on a liver biopsy specimen and reversal of portal blood flow by Doppler ultrasonography. Concomitant GI bleeding does not appear to worsen survival. Failure of the serum bilirubin level to decline after 7 (and probably 4) days of treatment with corticosteroids predicts nonresponse and poor long-term survival, as does the Lille model (which includes age, serum creatinine, serum albumin, prothrombin time [or INR], serum bilirubin on admission, and serum bilirubin on day 7). The MELD score used for cirrhosis and the Glasgow alcohol-associated hepatitis score (based on age, WBC count, BUN, prothrombin time ratio, and bilirubin level) also correlate with mortality from alcohol-associated hepatitis and have higher specificities than the discriminant function and Lille score. A scoring system based on age, serum bilirubin, INR, and serum creatinine (ABIC) has been proposed, and at least one study has shown that the development of AKI is the most accurate predictor of 90-day mortality. Another scoring system based on hepatic encephalopathy, systemic inflammatory response syndrome, and MELD score has also been reported to predict AKI and mortality. The combination of the MELD score and Lille model has been reported to be the best predictor of short-term mortality among the scoring systems. Histologic features associated with 90-day mortality include the degree of fibrosis and neutrophil infiltration, presence of megamitochondria, and bilirubinostasis.

B. Long-Term

The 3-year mortality rate of persons who recover from acute alcohol-associated hepatitis is 10 times greater than that of control individuals of comparable age; the 5-year mortality rate is as high as 85%. Histologically severe disease is associated with continued excessive mortality rates after 3 years, whereas the death rate is not increased after the same period in those whose liver biopsy specimens show only mild alcohol-associated hepatitis. Complications of portal hypertension (ascites, variceal bleeding, hepatorenal syndrome), coagulopathy, and severe jaundice following recovery from acute alcohol-associated hepatitis also suggest a poor long-term prognosis.

The most important long-term prognostic factor is continued excessive drinking. The overall 10-year survival among all persons with alcohol-associated liver disease is 88% among those who are abstinent compared with 73% in those who experience a relapse in drinking. There is no safe level of drinking in persons with alcohol-associated liver disease or other liver diseases. The risk of alcohol-associated cirrhosis is greater in women than in men and associated with obesity, cigarette smoking, chronic hepatitis C, and low vitamin D levels; the risk is inversely associated with coffee drinking. Alcohol-associated cirrhosis is a risk factor for hepatocellular carcinoma, and the risk is highest in carriers of the *C282Y* pathogenic variant for hemochromatosis or those with increased hepatic iron. A 6-month period of abstinence is generally required before liver transplantation is considered, although this requirement has been questioned and early liver transplantation has been performed in selected patients with alcohol-associated hepatitis, with good outcomes. Optimal candidates have adequate social support, do not smoke, have no psychosis or personality disorder, are adherent to therapy, and have regular appointments with a psychiatrist or psychologist who specializes in addiction treatment. Patients with alcohol-associated liver disease are at higher risk for posttransplant malignancy than those with other types of liver disease because of alcohol and tobacco use.

When to Refer

Refer patients with alcohol-associated hepatitis who require liver biopsy for diagnosis.

When to Admit

- Hepatic encephalopathy.
- INR greater than 1.6.
- Total bilirubin 10 mg/dL or more.
- Inability to maintain hydration.

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DRUG- & TOXIN-INDUCED LIVER INJURY

ESSENTIALS OF DIAGNOSIS

- Drug-induced liver injury can mimic viral hepatitis, biliary tract obstruction, or other types of liver disease.
- Clinicians must inquire about the use of many widely used therapeutic agents, including over-the-counter "natural" and herbal and dietary supplements, in any patient with liver disease.

General Considerations

Many therapeutic agents may cause drug-induced liver injury, with jaundice occurring in 30% of cases and up to 10% of patients with drug-induced liver injury dying or undergoing liver transplantation within 6 months of onset. In any patient with liver disease, the clinician must inquire carefully about the use of potentially hepatotoxic drugs or exposure to hepatotoxins, including over-the-counter herbal and dietary supplements. The medications most commonly implicated are antibiotics because of their widespread use. In some cases, coadministration of a second agent may increase the toxicity of the first (eg, isoniazid and rifampin, acetaminophen and alcohol, combinations of immune checkpoint inhibitors). The diagnosis often depends on exclusion of other causes of liver disease. A relationship between increased serum ALT levels in premarketing clinical trials and postmarketing reports of hepatotoxicity has been identified. Except for drugs used to treat tuberculosis and HIV infection, obeticholic acid, and possibly azithromycin, the risk of hepatotoxicity is not increased in patients with preexisting cirrhosis, but hepatotoxicity may be more severe and the outcome worse when it does occur. Older persons may be at higher risk for hepatotoxicity from certain agents, such as amoxicillin-clavulanic acid, isoniazid, and nitrofurantoin, and more likely to have persistent and cholestatic, rather than hepatocellular, injury compared with younger persons. Drug toxicity may be categorized based on pathogenesis or predominant histologic appearance. Drug-induced liver injury can mimic viral hepatitis, biliary tract obstruction, vanishing bile duct syndrome, or other types of liver disease (and vice versa). The development of jaundice in a patient with serum aminotransferase levels at least three times the upper limit of normal predicts a mortality rate of at least 10% ("Hy's Law"). A model based on the presence of comorbidities, the MELD score, and serum albumin has been reported to predict 6-month mortality.

Categorization by Pathogenesis

A. Direct Hepatotoxicity

Liver toxicity caused by this group of drugs is characterized by dose-related severity, a latent period following exposure, and susceptibility in all individuals. One example is acetaminophen (the toxicity of which is enhanced by fasting because of depletion of glutathione and by long-term alcohol use both because of depletion of glutathione and because of induction of cytochrome P450 2E1; and the toxicity of which is possibly reduced by statins, fibrates, and NSAIDs and acetylcysteine treatment). Other examples include alcohol, *Amanita phalloides* mushrooms, carbon tetrachloride, chloroform, heavy metals, mercaptopurine, niacin, obeticholic acid, plant alkaloids, phosphorus, pyrazinamide, tetracyclines, tipranavir, valproic acid, and vitamin A.

B. Idiosyncratic Reactions

Except for acetaminophen, most severe hepatotoxicity is idiosyncratic. Reactions of this type are (1) sporadic, (2) not related to dose above a general threshold of 100 mg/day, and (3) occasionally associated with features suggesting an allergic reaction, such as fever and eosinophilia (including drug rash with eosinophilia and systemic symptoms [DRESS] syndrome), which may be associated with a favorable outcome. In many instances, the drug is lipophilic, and toxicity results directly from a reactive metabolite that is produced only in certain individuals on a genetic basis. Illness tends to be more severe in Black persons than in White persons. Drug-induced liver injury may be observed only during postmarketing surveillance and not during preclinical trials. Examples include abacavir, abeparvovec, alemtuzumab, atabecestat, amiodarone, aspirin, carbamazepine, chloramphenicol, dapsone, diclofenac, disulfiram, duloxetine, ezetimibe, flavocoxid (a "medical food"), fluoroquinolones (levofloxacin and moxifloxacin, in particular), flutamide, halothane, isoniazid, ketoconazole, lamotrigine, methyldopa, natalizumab, nevirapine, oxacillin, phenytoin, pyrazinamide, quinidine, remdesivir, rivaroxaban, streptomycin, temozolomide, thiazolidinediones, tolvaptan, and perhaps tacrine. Statins, like all cholesterol-lowering agents, may cause serum aminotransferase elevations but rarely cause true hepatitis, and even more rarely cause acute liver failure, and are no longer considered contraindicated in patients with liver disease. Most acute idiosyncratic drug-induced liver injury is reversible with discontinuation of the offending agent. Risk factors for chronicity (longer than 1 year) are older age, dyslipidemia, and severe acute injury.

C. Indirect Hepatotoxicity

Indirect hepatotoxicity refers to liver injury that results when use of a drug leads to exacerbation of preexisting liver disease. An example is a flare of HBV infection in the setting of immunosuppressive therapy for a nonhepatic autoimmune disease.

Categorization by Histopathology

A. Cholestatic Injury

1. Noninflammatory—Drug-induced cholestasis results from inhibition or genetic deficiency of various hepatobiliary transporter systems. The following drugs cause cholestasis: anabolic steroids containing an alkyl or ethinyl

group at carbon 17, azathioprine, cetirizine, cyclosporine, diclofenac, estrogens, febuxostat, indinavir (increased risk of indirect hyperbilirubinemia in patients with Gilbert syndrome), mercaptopurine, methyltestosterone, tamoxifen, temozolomide, and ticlopidine.

2. Inflammatory—The following drugs cause inflammation of portal areas with bile duct injury (cholangitis [and, in some cases, bile duct loss]), often with allergic features such as eosinophilia: amoxicillin-clavulanic acid (among the most common causes of drug-induced liver injury), azathioprine, azithromycin, captopril, celecoxib, cephalosporins, chlorothiazide, chlorpromazine, chlorpropamide, erythromycin, mercaptopurine, pazopanib, penicillamine, prochlorperazine, semisynthetic penicillins (eg, cloxacillin), sulfadiazine, and temozolomide. Ketamine abuse may cause secondary biliary cirrhosis. Cholestatic and mixed cholestatic-hepatocellular toxicity is more likely than pure hepatocellular toxicity to lead to chronic liver disease.

B. Hepatocellular Injury

Medications that may result in acute or chronic hepatitis that is histologically and, in some cases, clinically similar to autoimmune hepatitis include minocycline and nitrofurantoin, most commonly, as well as aspirin, isoniazid (increased risk in HBV and HCV carriers), methyldopa, NSAIDs, propylthiouracil, terbinafine, tumor necrosis factor inhibitors, and varenicline. Histologic features that favor a drug cause include portal tract neutrophils and hepatocellular cholestasis. Hepatitis also can occur in patients taking cocaine, diclofenac, dimethyl fumarate, efavirenz, imatinib mesylate, ipilimumab, nivolumab, and other checkpoint inhibitors, which may also cause cholangitis, methylenedioxymethamphetamine (MDMA; ecstasy), nefazodone (has a black box warning for a potential to cause liver failure), nevirapine (like other HIV protease inhibitors, increased risk in HBV and HCV carriers), pioglitazone, ritonavir (greater rate than other HIV protease inhibitors), rosiglitazone, saquinavir, sulfonamides, telithromycin, tocilizumab, and zafirlukast, as well as a variety of alternative remedies (eg, black cohosh, chaparral, garcinia cambogia, germander, green tea extract, Herbalife products, Hydroxycut, jin bu huan, kava, saw palmetto, skullcap, usnic acid, and other traditional Chinese herbal preparations), in addition to dietary supplements (eg, 1,3-dimethylamylamine in OxyELITE Pro, a weight loss supplement withdrawn from the US market).

C. Other Reactions

1. Fatty liver—

A. Macrovesicular—This type of liver injury may be produced by alcohol, amiodarone, corticosteroids, haloperidol, irinotecan, lomitapide, methotrexate, mipomersen, tamoxifen, vinyl chloride (in exposed workers), zalcitabine, and possibly oxaliplatin.

B. Microvesicular—Often resulting from mitochondrial injury, microvesicular steatosis is associated with aspirin (Reye syndrome), didanosine, linezolid, stavudine, tetracyclines, valproic acid, and zidovudine.

2. Granulomas—Allopurinol, hydralazine, pembrolizumab and other immune checkpoint inhibitors, phenytoin, pyrazinamide, quinidine, quinine, sulfasalazine, and vemurafenib can lead to granulomas and, in some cases, granulomatous hepatitis.

3. Fibrosis and cirrhosis—Methotrexate and vitamin A are associated with fibrosis and cirrhosis.

4. Sinusoidal obstruction syndrome (veno-occlusive disease)—This disorder may result from treatment with antineoplastic agents (eg, pre–bone marrow transplant, busulfan, gemtuzumab ozogamicin, inotuzumab ozogamicin, oxaliplatin), mycophenolate mofetil, and pyrrolizidine alkaloids (eg, comfrey).

5. Peliosis hepatis (blood-filled cavities)—Peliosis hepatis may be caused by anabolic steroids and oral contraceptive steroids as well as azathioprine and mercaptopurine, which may also cause nodular regenerative hyperplasia and other forms of liver injury.

6. Nodular regenerative hyperplasia—Nodular regenerative hyperplasia may be caused by azathioprine, 5-fluorouracil, oxaliplatin, and thioguanine.

7. Neoplasms—Neoplasms may result from therapy with oral contraceptive steroids, including estrogens (hepatic adenoma but not focal nodular hyperplasia) and vinyl chloride (angiosarcoma).

When to Refer

Refer patients with drug- and toxin-induced hepatitis who require liver biopsy for diagnosis.

When to Admit

Patients with liver failure should be hospitalized.

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NONALCOHOLIC FATTY LIVER DISEASE

ESSENTIALS OF DIAGNOSIS

- Often asymptomatic.
- Elevated aminotransferase levels, hepatomegaly, or steatosis on ultrasonography.
- Predominantly macrovesicular steatosis with or without inflammation and fibrosis on liver biopsy.

General Considerations

NAFLD is estimated to affect 37% of the US adult population and has increased in incidence at least fivefold since the late 1990s. Even adolescents and young adults may be affected. The principal causes of NAFLD are obesity (present in 40% or more of affected patients), diabetes mellitus (in 20% or more), and hypertriglyceridemia (in 20% or more) in association with insulin resistance as part of the metabolic syndrome. In fact, the alternative designation "metabolic-associated (or metabolic dysfunction–associated) fatty liver disease" (MAFLD) has been proposed. The risk of NAFLD in persons with metabolic syndrome is 4 to 11 times higher than that of persons without insulin resistance. Nonobese persons (more frequently Asians) account for 10–20% of persons with NAFLD and have metabolic profiles characteristic of insulin resistance. Other causes of fatty liver include corticosteroids, amiodarone, diltiazem, methotrexate, tamoxifen, irinotecan, oxaliplatin, antiretroviral therapy, toxins (vinyl chloride, carbon tetrachloride, yellow phosphorus), endocrinopathies such as Cushing syndrome and hypopituitarism, polycystic ovary syndrome, hypothyroidism, hypobetalipoproteinemia and other metabolic disorders, obstructive sleep apnea (with chronic intermittent hypoxia), excessive dietary fructose consumption, malnutrition, starvation and refeeding syndrome, and total parenteral nutrition. NAFLD may be a predisposing factor in liver injury caused by some drugs. The risk of NAFLD is increased in persons with psoriasis and appears to correlate with the activity of psoriasis. Soft drink consumption and cholecystectomy have been reported to be associated with NAFLD. Physical activity protects against the development of NAFLD.

In addition to macrovesicular steatosis, histologic features may include focal infiltration by polymorphonuclear neutrophils and Mallory hyalin, a picture indistinguishable from that of alcohol-associated hepatitis and referred to as nonalcoholic steatohepatitis (NASH), which affects 3–6% of the US population and leads to cirrhosis in approximately 20% of affected persons. In patients with NAFLD, older age, obesity, and diabetes mellitus are risk factors for advanced hepatic fibrosis and cirrhosis, whereas coffee consumption reduces the risk. The frequency and severity of NAFLD is greater in men than in women during reproductive age, but after menopause the frequency is higher in women than men, suggesting that estrogen is protective. However, in women, synthetic hormone use (oral contraceptives and hormone replacement therapy) increases the histologic severity of NASH. Cirrhosis caused by NASH appears to be uncommon in Black persons. Persons with NAFLD are at increased risk for CVD, CKD, and colorectal cancer.

Microvesicular steatosis is seen with Reye syndrome, with toxicity caused by didanosine, stavudine, linezolid, valproic acid, or high-dose tetracycline, and with acute fatty liver of pregnancy and may result in acute liver failure.

Clinical Findings

A. Symptoms and Signs

Most patients with NAFLD are asymptomatic or have mild right upper quadrant discomfort. Hepatomegaly is present in up to 75% of patients, but stigmata of chronic liver disease are uncommon. Signs of portal hypertension generally signify advanced liver fibrosis or cirrhosis, but occasionally occur in patients with mild or no fibrosis and severe steatosis.

B. Laboratory Findings

Laboratory studies may show mildly elevated aminotransferase and alkaline phosphatase levels; however, laboratory values may be normal in up to 80% of persons with hepatic steatosis. In contrast to alcohol-associated liver disease, the ratio of ALT to AST is almost always greater than 1.0 in NAFLD, but it decreases, often to less than 1.0, as advanced fibrosis and cirrhosis develop. Antinuclear or smooth muscle antibodies and an elevated serum ferritin level may each be detected in 30% of patients with NASH. Iron deficiency is also common and associated with female sex, obesity, increased waist circumference, diabetes mellitus, and persons who are Black or Native Americans.

C. Imaging

Macrovascular steatosis may be demonstrated on ultrasonography, CT, or MRI. However, imaging does not distinguish steatosis from steatohepatitis or detect fibrosis. Where available, MRI-proton density fat fraction or magnetic resonance spectroscopy allows hepatic fat content to be quantitated and appears to correlate with the risk of fibrosis progression; ultrasound or magnetic resonance elastography to assess liver stiffness can be used to estimate hepatic fibrosis.

D. Liver Biopsy and Risk Scores

Percutaneous liver biopsy is diagnostic and has been the standard approach to assessing the degree of inflammation and fibrosis. The risks of the procedure must be balanced against the impact of the added information on management decisions and assessment of prognosis. Liver biopsy is generally not recommended in asymptomatic persons with unsuspected hepatic steatosis detected on imaging but normal liver biochemistry test results. The histologic spectrum of NAFLD includes fatty liver, isolated portal fibrosis, steatohepatitis, and cirrhosis. Noninvasive approaches to the assessment of fibrosis are now preferred, with liver biopsy reserved when results of noninvasive testing are inconclusive. The FIB-4 score is often used particularly to exclude advanced fibrosis because of its simplicity. It is based on age, platelet count, and serum AST and ALT levels. A risk score for predicting advanced fibrosis, known as BARD, is based on BMI more than 28, AST/ALT ratio 0.8 or more, and diabetes mellitus; it has a high negative predictive value (ie, a low score reliably excludes advanced fibrosis). Another risk score for advanced fibrosis, the NAFLD Fibrosis Score (http://nafldscore.com) based on age, hyperglycemia, BMI, platelet count, albumin, and AST/ALT ratio, has a positive predictive value of over 80% and identifies patients at increased risk for liver-related complications and death. A clinical scoring system to predict the likelihood of NASH in morbidly obese persons includes six predictive factors: hypertension, type 2 diabetes mellitus, sleep apnea, AST greater than 27 U/L

(0.54 mckat/L), ALT greater than 27 U/L (0.54 mckat/L), and persons who are not Black. The role of liver stiffness measurement by elastography to assess the fibrosis stage continues to evolve; in general, results are less accurate in obese than in nonobese persons.

Treatment

Treatment consists of lifestyle changes to remove or modify the offending factors often in the context of a multidisciplinary clinic. Weight loss, dietary fructose restriction, increased dietary fiber, and moderate exercise (through reduction of abdominal obesity) often lead to improvement in liver biochemical tests and steatosis in obese patients with NAFLD. A Mediterranean diet can reduce liver fat without weight loss and is often recommended. Loss of 5% of body weight appears necessary to improve steatosis, loss of greater than or equal to 7% improves steatohepatitis, and loss of greater than or equal to 10% improves fibrosis. Exercise may reduce liver fat with minimal or no weight loss and no reduction in ALT levels. Resistance training and aerobic exercise are equally effective in reducing hepatic fat content in patients with NAFLD and type 2 diabetes mellitus. Although avoidance of alcohol is recommended, modest wine consumption may not be detrimental in nonsmokers. Various drugs for the treatment of NASH are under study. Vitamin E 800 IU/day (to reduce oxidative stress) appears to be of benefit in patients with NASH who do not have diabetes mellitus. There is controversy as to whether vitamin E increases the risk of prostate cancer in men and hemorrhagic stroke; moreover, the benefit is often not sustained. Thiazolidinediones reverse insulin resistance and, in most relevant studies, have improved both serum aminotransferase levels and histologic features of steatohepatitis but lead to weight gain. Metformin, which reduces insulin resistance, improves abnormal liver chemistries but may not reliably improve liver histology. Pentoxifylline improves liver biochemical test levels but is associated with a high rate of side effects, particularly nausea. Ursodeoxycholic acid, 12–15 mg/kg/day, has not consistently resulted in biochemical and histologic improvement in patients with NASH but may be effective when given in combination with vitamin E. Hepatic steatosis due to total parenteral nutrition may be ameliorated—and perhaps prevented—with supplemental choline. Obeticholic acid, a farnesoid X receptor agonist that has been approved for the treatment of PBC, has been shown to improve liver fibrosis in patients with NASH. Statins are not contraindicated in persons with NAFLD and may protect against histologic progression in some patients. Bariatric surgery may be considered in patients with a BMI greater than 35 and leads to histologic regression of NASH in most patients (but worsening in a few). Liver transplantation is indicated in appropriate candidates with advanced cirrhosis caused by NASH, the third most common (and most rapidly increasing) indication for liver transplantation in the United States. Liver transplantation for NASH with advanced cirrhosis may be associated with increased mortality from CVD and sepsis compared with liver transplantation for other indications.

Prognosis

Fatty liver often has a benign course and is readily reversible with discontinuation of alcohol (or no more than one glass of wine per day, which has been reported in some, but not other, studies to reduce the frequency of NASH in persons with NAFLD), or treatment of other underlying conditions; if untreated, fibrosis progresses at an average rate of one stage every 14 years, with 20% of patients progressing more rapidly. In patients with NAFLD, the likelihood of NASH is increased by the following factors: obesity, older age, ethnicity other than Black, female sex, diabetes mellitus, hypertension, higher ALT or AST level, higher AST/ALT ratio, low platelet count, elevated fasting C-peptide level, and a high ultrasound steatosis score. NASH may be associated with hepatic fibrosis in 40% of cases with progression at a rate of one stage every 7 years; cirrhosis develops in 9–25%; and decompensated cirrhosis occurs in 30–50% of cirrhotic patients over 10 years. The course may be more aggressive in diabetic persons than in nondiabetic persons. In the United States, NAFLD is associated with 8% of all-cause mortality and more than one-third of deaths associated with liver disease and with diabetes mellitus. Risk factors for fibrosis in patients with fatty liver without NASH are severe steatosis and the I148M variant of the *PNPLA3* gene. Heterozygous alpha-1-antitrypsin deficiency also appears to be a risk factor for fibrosis in patients with NASH. Mortality is increased in patients with NAFLD, correlates with fibrosis stage, and is the result of CVD and malignancy (including hepatocellular carcinoma, colorectal cancer, and breast cancer) as well as liver disease. Risk factors for mortality are older age, male sex, White race, the I148M variant of the *PNPLA3* gene, smoking, higher BMI, hypertension, diabetes mellitus, and advanced fibrosis stage. In the general population, in fact, both excess adiposity and reduced activity are significant predictors of liver-related mortality. Steatosis is a cofactor for the progression of fibrosis in patients with other causes of chronic liver disease, such as hepatitis C, and NAFLD appears to be a risk factor for CKD. Hepatocellular carcinoma is a complication of cirrhosis caused by NASH, as it is for other causes of cirrhosis, and has been reported even in the absence of cirrhosis. NASH accounts for a substantial percentage of cases labeled as cryptogenic cirrhosis and can recur following liver transplantation. Central obesity is an independent risk factor for death from cirrhosis of any cause.

When to Refer

Refer patients with NAFLD who require liver biopsy for diagnosis and those with evidence of advanced fibrosis for management.

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CIRRHOSIS

ESSENTIALS OF DIAGNOSIS

- Result of injury that leads to both fibrosis and regenerative nodules.
- May be reversible if cause is removed.
- The clinical features result from hepatic cell dysfunction, portosystemic shunting, and portal hypertension.

General Considerations

Cirrhosis is the result of hepatocellular injury with inflammation that leads to both fibrosis and regenerative nodules throughout the liver. The prevalence rate is 0.27%, with an estimated 1.5 billion persons having chronic liver disease and 2.14 million liver-related deaths worldwide. Hospitalization rates for cirrhosis and portal hypertension are rising in the United States, and patients with chronic liver disease have longer hospital stays, more readmissions, and less access to post-acute care than patients with other chronic diseases. Causes include chronic viral hepatitis; alcohol; drug toxicity; autoimmune and metabolic liver diseases, including NAFLD; and miscellaneous disorders. Celiac disease appears to be associated with an increased risk of cirrhosis. Many patients have more than one risk factor (eg, chronic hepatitis and alcohol use) and likely genetic predisposition. Mexican American and Black persons have a higher frequency of cirrhosis than White persons because of a higher rate of risk factors. In persons at increased risk for liver injury (eg, heavy alcohol use, obesity, iron overload), higher coffee and tea consumption and statin use reduce the risk of cirrhosis.

Clinically, cirrhosis is considered to progress through three stages that correlate with the thickness of fibrous septa: compensated, compensated with varices, and decompensated (ascites, variceal bleeding, encephalopathy, or jaundice).

A diagnosis of acute-on-chronic liver failure should be made in a patient with cirrhosis and acute decompensation (new or worsening ascites, GI hemorrhage, overt encephalopathy, worsening nonobstructive jaundice, or bacterial infection associated with other organ failure). Precipitating factors include infections, hemodynamic instability, heavy alcohol use, and drug hepatotoxicity.

Clinical Findings

A. Symptoms and Signs

The clinical features of cirrhosis result from hepatocyte dysfunction, portosystemic shunting, and portal hypertension. Patients may have no symptoms for long periods. The onset of symptoms may be insidious or, less often, abrupt. Fatigue, disturbed sleep, muscle cramps, and weight loss are common. In advanced cirrhosis, anorexia is usually present and may be extreme, with associated nausea and occasional vomiting, as well as reduced muscle strength and exercise capacity. Abdominal pain may be present and is related either to hepatic enlargement and stretching of Glisson capsule or to the presence of ascites. Abdominal wall hernias occur in 20% of persons with cirrhosis. Menstrual abnormalities (usually amenorrhea), erectile dysfunction, loss of libido, sterility, and gynecomastia may occur. Hematemesis is the presenting symptom in 15–25%. The risk of falls is increased in patients with cirrhosis and the falls are associated with mortality.

Skin manifestations consist of spider telangiectasias (invariably on the upper half of the body), palmar erythema (mottled redness of the thenar and hypothenar eminences), Dupuytren contractures, and Terry nails. Evidence of vitamin deficiencies (glossitis and cheilosis) is common. Weight loss, wasting (due to sarcopenia), and the appearance of chronic illness are present in advanced cirrhosis. Jaundice—usually not an initial sign—is mild at first, increasing in severity during the later stages of the disease. In 70% of cases, the liver is enlarged, palpable, and firm if not hard and has a sharp or nodular edge; the left lobe may predominate. Splenomegaly is present in 35–50% of cases and is associated with an increased risk of complications of portal hypertension. The superficial veins of the abdomen and thorax are dilated, reflecting the intrahepatic obstruction to portal blood flow, as do rectal varices. The abdominal wall veins fill from below when compressed. Ascites, pleural effusions, peripheral edema, and ecchymoses are late findings. Ascites is classified as grade 1, or mild, when it is detectable only by ultrasound; grade 2, or moderate, when associated with symmetrical abdominal distention; and grade 3, or gross, when associated with marked abdominal distention. Encephalopathy, characterized by day-night reversal, asterixis, tremor, dysarthria, delirium, drowsiness, and, ultimately, coma, also occurs late in the course except when precipitated by an acute hepatocellular insult or an episode of GI bleeding or infection. Fever is present in up to 35% of patients and usually reflects associated alcohol-associated hepatitis, spontaneous bacterial peritonitis, or another intercurrent infection.

B. Laboratory Findings

Laboratory abnormalities are either absent or minimal in early or compensated cirrhosis. Anemia, a frequent finding, is often macrocytic; causes include suppression of erythropoiesis by alcohol as well as folate deficiency, hemolysis, hypersplenism, and occult or overt blood loss from the GI tract. The WBC count may be low, reflecting hypersplenism, or high, suggesting infection. Thrombocytopenia, the most common cytopenia in cirrhotic patients, is

secondary to alcohol-induced marrow suppression, sepsis, folate deficiency, or splenic sequestration. Prolongation of the prothrombin time may result from reduced levels of clotting factors (except factor VIII). However, bleeding risk correlates poorly with the prothrombin time because of concomitant abnormalities of fibrinolysis, and among hospitalized patients under age 45, cirrhosis is associated with an increased risk of venous thromboembolism.

Blood chemistries reflect hepatocellular injury and dysfunction, manifested by modest elevations of AST and alkaline phosphatase and progressive elevation of the bilirubin. Serum albumin decreases as the disease progresses; gamma-globulin levels are increased and may be as high as in autoimmune hepatitis. The risk of diabetes mellitus is increased in patients with cirrhosis, particularly when associated with HCV infection, alcoholism, hemochromatosis, or NAFLD. Vitamin D deficiency has been reported in as many as 91% of patients with cirrhosis. In cirrhosis of all causes, the following are common: (1) blunted cardiac inotropic and chronotropic responses to exercise, stress, and drugs, (2) prolongation of the QT interval in the setting of a hyperkinetic circulation, and (3) systolic and diastolic ventricular dysfunction in the absence of other known causes of cardiac disease ("cirrhotic cardiomyopathy"). Relative adrenal insufficiency appears to be common in patients with advanced cirrhosis, even in the absence of sepsis, and in those with acute-on-chronic liver failure.

C. Imaging

Ultrasonography is helpful for assessing liver size and detecting ascites or hepatic nodules, including small hepatocellular carcinomas. Together with a Doppler study, it may establish patency of the splenic, portal, and hepatic veins. Hepatic nodules are characterized further by contrast-enhanced CT or MRI. Nodules indeterminant for malignancy may be biopsied under ultrasound or CT guidance.

D. Liver Biopsy

Liver biopsy may show inactive cirrhosis (fibrosis with regenerative nodules) with no specific features to suggest the underlying cause. Alternatively, there may be additional features of alcohol-associated liver disease, chronic hepatitis, NASH, or other specific causes of cirrhosis. Liver biopsy may be performed by laparoscopy or, in patients with coagulopathy and ascites, by a transjugular or endoscopic ultrasonographic approach. Combinations of routine blood tests (eg, AST, platelet count), including the FibroSure test, serum markers of hepatic fibrosis (eg, hyaluronic acid, amino-terminal propeptide of type III collagen, tissue inhibitor of matrix metalloproteinase 1), and ultrasound or magnetic resonance elastography are potential alternatives to liver biopsy for the diagnosis or exclusion of cirrhosis. In persons with chronic hepatitis C, for example, a low FibroSure or elastography score reliably excludes advanced fibrosis, a high score reliably predicts advanced fibrosis, and intermediate scores are inconclusive. The combination of increased liver stiffness and a platelet count below 150,000/mcL (150×10^9/L) is an indicator of clinically significant portal hypertension.

E. Other Tests

Esophagogastroduodenoscopy confirms the presence of varices and detects specific causes of bleeding in the esophagus, stomach, and proximal duodenum. In selected cases, wedged hepatic vein pressure measurement may establish the presence and cause of portal hypertension.

Differential Diagnosis

The most common causes of cirrhosis are alcohol, chronic hepatitis C infection, NAFLD, and hepatitis B infection. Hemochromatosis is the most commonly identified genetic disorder that causes cirrhosis. Other diseases associated with cirrhosis include Wilson disease, alpha-1-antitrypsin (alpha-1-antiprotease) deficiency, and celiac disease. PBC occurs more frequently in women than men. Secondary biliary cirrhosis may result from chronic biliary obstruction due to a stone, stricture, or neoplasm. Heart failure and constrictive pericarditis may lead to hepatic fibrosis ("cardiac cirrhosis") complicated by ascites. Hereditary hemorrhagic telangiectasia can lead to portal hypertension because of portosystemic shunting and nodular transformation of the liver as well as high-output heart failure. Many cases of cirrhosis are "cryptogenic," in which unrecognized NAFLD may play a role.

Complications

Upper GI tract bleeding may occur from varices, portal hypertensive gastropathy, or gastroduodenal ulcer (see Chapter 15). Varices may also result from portal vein thrombosis, which may complicate cirrhosis. Liver failure may be precipitated by alcoholism, surgery, and infection. Hepatic Kupffer cell (reticuloendothelial) dysfunction and decreased opsonic activity lead to an increased risk of systemic infection (which may be increased further by the use of PPIs, which increase mortality fourfold). These infections include nosocomial infections, which may be classified as spontaneous bloodstream infections, UTIs, pulmonary infections, spontaneous bacterial peritonitis, *Clostridioides difficile* infection, and intervention-related infections. These nosocomial infections are increasingly caused by multidrug-resistant bacteria. Osteoporosis occurs in 12–55% of patients with cirrhosis. The risk of hepatocellular carcinoma is increased greatly in persons with cirrhosis (see Chapter 39). Varices, ascites, and encephalopathy may arise when there is clinically significant portal hypertension (hepatic venous pressure gradient greater than 10 mm Hg).

Treatment

A. General Measures

Most important is abstinence from alcohol. The diet should be palatable, with adequate calories (20–40 kcal/kg body weight per day depending on the patient's BMI and the presence or absence of malnutrition) and protein (1.2–1.5 g/kg/day depending on the presence or absence of malnutrition) and, if there is fluid retention, sodium restriction. In the presence of hepatic encephalopathy, protein intake should be reduced to no less than 60–80 g/day.

Vitamin supplementation is desirable. Muscle cramps may be helped by L-carnitine, 300 mg orally four times a day, calcium, quinidine, baclofen, muscle relaxants, or intravenous albumin. In patients with clinically significant portal hypertension, carvedilol, a nonselective beta receptor antagonist with alpha-1 blocking activity, appears to reduce the frequency of decompensating events, although it may lead to hypotension particularly in patients with decompensated cirrhosis. Patients with cirrhosis should receive the HAV, HBV, pneumococcal, and COVID-19 vaccines and a yearly influenza vaccine. Liver transplantation in appropriate candidates is curative. Care coordination and palliative care, when appropriate, have been shown to improve outcomes and reduce readmission rates.

B. Treatment of Complications

1. Ascites and edema—Diagnostic paracentesis is indicated for patients who have new ascites or who have been hospitalized for a complication of cirrhosis; it reduces mortality, especially if performed within 12 hours of admission. Serious complications of paracentesis, including bleeding, infection, or bowel perforation, occur in 1.6% of procedures and are associated with therapeutic (vs diagnostic) paracentesis and possibly with Child-Pugh class C, a platelet count less than 50,000/mcL (50×10^9/L), and alcohol-associated cirrhosis. In patients with coagulopathy, however, pre-paracentesis prophylactic transfusions are not necessary. In addition to a cell count and culture, the ascitic albumin level should be determined: a serum-ascites albumin gradient (serum albumin minus ascitic fluid albumin) greater than or equal to 1.1 suggests portal hypertension. An elevated ascitic adenosine deaminase level is suggestive of tuberculous peritonitis, but the sensitivity of the test is reduced in patients with portal hypertension. Occasionally, cirrhotic ascites is chylous (rich in triglycerides); other causes of chylous ascites are malignancy, tuberculosis, and recent abdominal surgery or trauma.

In individuals with ascites, the urinary sodium concentration is often less than 10 mEq/L (10 mmol/L). Free water excretion is also impaired in cirrhosis, and hyponatremia may develop.

In all patients with cirrhotic ascites, dietary sodium intake may initially be restricted to 2000 mg/day; the intake of sodium may be liberalized slightly after diuresis ensues. NSAIDs are contraindicated, and aminoglycosides, ACE inhibitors, and angiotensin II antagonists should be avoided. In some patients, ascites diminishes promptly with bed rest and dietary sodium restriction alone. Fluid intake is often restricted (to 800–1000 mL/day) in patients with hyponatremia. Treatment of severe hyponatremia (serum sodium less than 120 mEq/L [120 mmol/L]) with vasopressin receptor antagonists (eg, intravenous conivaptan, 20 mg daily) can be considered, but such treatment is expensive, causes thirst, and does not improve survival; oral tolvaptan is contraindicated in patients with liver disease because of potential hepatotoxicity. Long-term intravenous administration of albumin has been reported to improve 18-month survival in patients with cirrhotic ascites.

a. Diuretics—Spironolactone, generally in combination with furosemide, should be used in patients who do not respond to salt restriction alone. The dose of spironolactone is initially 100 mg orally daily and may be increased by 100 mg every 3–5 days (up to a maximal conventional daily dose of 400 mg/day, although higher doses have been used) until diuresis is achieved, typically preceded by a rise in the urinary sodium concentration. A "spot" urine sodium concentration that exceeds the potassium concentration correlates with a 24-hour sodium excretion greater than 78 mmol/day, which predicts diuresis in patients adherent to a salt-restricted diet. Monitoring for hyperkalemia is important. In patients who cannot tolerate spironolactone because of side effects, such as painful gynecomastia, amiloride (another potassium-sparing diuretic) may be used in a starting dose of 5–10 mg orally daily. Diuresis is augmented by the addition of a loop diuretic such as furosemide. This potent diuretic, however, will maintain its effect even with a falling GFR, with resulting prerenal azotemia. The dose of oral furosemide is increased in concert with spironolactone and ranges from 40 mg/day to 160 mg/day, and blood pressure, urinary output, mental status, and serum electrolytes (especially potassium) should be monitored in patients taking the drug. The goal of weight loss in the ascitic patient without associated peripheral edema should be no more than 1–1.5 lb/day (0.5–0.7 kg/day).

b. Large-volume paracentesis—In patients with massive ascites and respiratory compromise, ascites which is refractory to diuretics ("diuretic resistant"), or which produces intolerable diuretic side effects ("diuretic intractable") (affecting 5–10% of patients with cirrhosis and ascites), large-volume paracentesis (more than 5 L) is effective. Intravenous albumin concomitantly at a dosage of 6–8 g/L of ascites fluid removed protects the intravascular volume and may prevent post-paracentesis circulatory dysfunction, although the usefulness of this practice is debated and albumin is expensive. Large-volume paracentesis can be repeated daily until ascites is largely resolved and may decrease the need for hospitalization. If possible, diuretics should be continued in the hope of preventing recurrent ascites.

c. Transjugular intrahepatic portosystemic shunt (TIPS)—TIPS is an effective treatment of variceal bleeding refractory to standard therapy (eg, endoscopic band ligation) and has shown benefit in the treatment of severe refractory ascites, specifically in patients on maximum diuretic therapy who require at least three large-volume paracenteses per year. The technique involves insertion of an expandable metal stent between a branch of the hepatic vein and the portal vein over a catheter inserted via the internal jugular vein. Increased renal sodium excretion and control of ascites refractory to diuretics can be achieved in about 75% of selected cases. The success rate is lower in patients with underlying CKD. TIPS may be considered for refractory hepatic hydrothorax (translocation of ascites across the diaphragm to the pleural space); video-assisted thoracoscopy with pleurodesis using talc may be effective when TIPS is contraindicated. Complications of

TIPS include hepatic encephalopathy in 20–30% of cases, infection, shunt stenosis in up to 60% of cases, and shunt occlusion in up to 30% of cases when bare stents are used; polytetrafluoroethylene-covered stents are associated with long-term patency rates of 80–90%. Long-term patency often requires periodic shunt revisions. In most cases, patency can be maintained by balloon dilation, local thrombolysis, or placement of an additional stent. TIPS is particularly useful in patients who require short-term control of variceal bleeding or ascites until liver transplantation can be performed. In patients with refractory ascites, TIPS results in lower rates of ascites recurrence and hepatorenal syndrome but a higher rate of hepatic encephalopathy (the frequency of which is reduced with prophylactic rifaximin) than occurs with repeated large-volume paracentesis; benefits to sarcopenia and to survival have been demonstrated. CKD, diastolic cardiac dysfunction, refractory encephalopathy, and hyperbilirubinemia (greater than 5 mg/dL [85.5 mcmol/L]) are associated with mortality after TIPS, and patients with a serum bilirubin greater than 3 mg/dL (50 mcmol/L), platelets less than 75,000/mcL (75×10^9/L), preexisting encephalopathy, active infection, severe heart failure, or severe pulmonary hypertension may not benefit from TIPS.

2. Spontaneous bacterial peritonitis—Spontaneous bacterial peritonitis is heralded by abdominal pain, increasing ascites, fever, and progressive encephalopathy in a patient with cirrhotic ascites; symptoms are typically mild. (Analogously, spontaneous bacterial empyema may complicate hepatic hydrothorax and is managed similarly.) Risk factors in cirrhotic patients with ascites include gastroesophageal variceal bleeding and possibly use of a PPI. Paracentesis reveals an ascitic fluid with, most commonly, a total white cell count of up to 500 cells/mcL (0.5×10^9/L) with a high polymorphonuclear (PMN) cell count (250/mcL [0.25×10^9/L] or more) and a protein concentration of 1 g/dL (10 g/L) or less. Cultures of ascites give the highest yield—80–90% positive—when specialized culture bottles are inoculated at the bedside. Common isolates are *Escherichia coli* and *Streptococcus* spp. Gram-positive cocci are the most common isolates in patients who have undergone an invasive procedure such as central venous line placement, and the frequency of enterococcal isolates is increasing. Anaerobes are uncommon. Pending culture results, if there are 250 or more PMNs/mcL or symptoms or signs of infection, intravenous antibiotic therapy should be initiated with cefotaxime, 2 g every 8–12 hours for at least 5 days. Alternative choices include ceftriaxone, amoxicillin-clavulanic acid, and levofloxacin (in patients not receiving fluoroquinolone prophylaxis). Oral ofloxacin, 400 mg twice daily for 7 days, or, in a patient not already taking a fluoroquinolone for prophylaxis against bacterial peritonitis, a 2-day course of intravenous ciprofloxacin, 200 mg twice daily, followed by oral ciprofloxacin, 500 mg twice daily for 5 days, may be effective alternative regimens in selected patients. Piperacillin-tazobactam is recommended for patients with risk factors for multidrug-resistant organisms, including hospital-acquired spontaneous bacterial peritonitis, and specific therapy should be guided by local resistance patterns. Vancomycin should be added in patients with prior bacterial peritonitis or a positive surveillance swab for methicillin-resistant *Staphylococcus aureus*. Daptomycin should be added in patients with a positive surveillance swab for vancomycin-resistant enterococcus. Meropenem can be used in patients with current or recent exposure to piperacillin-tazobactam. In patients with spontaneous bacterial peritonitis in the setting of acute-on-chronic liver failure, treatment with meropenem and daptomycin is recommended. Supplemental administration of intravenous albumin, 1.5 g/kg at diagnosis and 1 g/kg on day 3 (which may have anti-inflammatory effects in addition to expanding plasma volume), prevents further renal impairment and reduces mortality, particularly in patients with a serum creatinine greater than 1 mg/dL (83.3 mcmol/L), BUN greater than 30 mg/dL (10.8 mmol/L), or total bilirubin greater than 4 mg/dL (68.4 mcmol/L). Nonselective beta-blockers should be held in patients who develop hypotension (mean arterial pressure less than 65 mm Hg) or AKI. Given the increasing failure of initial empiric antibiotic therapy, response to therapy should be documented by a decrease in the PMN count of at least 25% on repeat paracentesis 48 hours after initiation of therapy. The overall mortality rate is high—up to 30% during hospitalization and up to 70% by 1 year. Mortality may be predicted by the 22/11 model: MELD score greater than 22 and peripheral WBC count higher than 11,000/mcL (11×10^9/L). Another model predictive of mortality includes the BUN, WBC count, Child-Pugh score, and mean arterial pressure. Patients with cirrhosis and septic shock have a high frequency of relative adrenal insufficiency, which if present requires administration of hydrocortisone.

In survivors of bacterial peritonitis, the risk of recurrent peritonitis may be decreased by long-term ciprofloxacin (eg, 500 mg orally once per day), norfloxacin (400 mg orally daily; no longer available in the United States), or trimethoprim-sulfamethoxazole (eg, one double-strength tablet once per day). In cases of recurrent peritonitis, the causative organism is often resistant to fluoroquinolones and may become multidrug resistant in some cases. In high-risk cirrhotic patients without prior peritonitis (eg, those with an ascitic protein less than 1.5 g/dL and serum bilirubin greater than 3 mg/dL (51.3 mcmol/L), serum creatinine greater than 1.2 mg/dL (99.96 mcmol/L), BUN 25 mg/dL (9 mmol/L) or more, sodium 130 mEq/L (130 mmol/L) or less, or Child-Pugh score of 9 or more, the risk of peritonitis, hepatorenal syndrome, and mortality for at least 1 year may be reduced by prophylactic trimethoprim-sulfamethoxazole, one double-strength tablet once per day, ciprofloxacin, 500 mg once per day, or norfloxacin, 400 mg orally once a day (though not in the United States). In patients hospitalized for acute variceal bleeding, intravenous ceftriaxone (1 g per day), followed by oral trimethoprim-sulfamethoxazole (one double-strength tablet once per day) or ciprofloxacin (500 mg every 12 hours), for a total of 7 days, reduces the risk of bacterial peritonitis.

3. Hepatorenal syndrome—Hepatorenal syndrome occurs in up to 10% of patients with advanced cirrhosis and ascites. It is characterized by azotemia (increase in serum

creatinine level of greater than 0.3 mg/dL [26.5 mcmol/L]) within 48 hours or increase by 50% or more from baseline within the previous 7 days or a urine volume less than 0.5 mL/kg/hour for 6 hours or longer in the absence of (1) current or recent nephrotoxic drug use, (2) macroscopic signs of structural kidney injury, or (3) shock and failure of kidney function to improve following 2 days of diuretic withdrawal and volume expansion with albumin, 1 g/kg up to a maximum of 100 g/day. Oliguria, hyponatremia, and a low urinary sodium concentration are typical features. Hepatorenal syndrome is diagnosed only when other causes of acute kidney injury (including prerenal azotemia and ATN) have been excluded. AKI-hepatorenal syndrome (formerly type 1 hepatorenal syndrome) is typically associated with at least doubling of the serum creatinine to a level greater than 2.5 mg/dL (208.25 mcmol/L) or by halving of the creatinine clearance to less than 20 mL/minute (0.34 mL/s/1.73 m^2 BSA) in less than 2 weeks. CKD (or non-AKI)-hepatorenal syndrome (formerly type 2 hepatorenal syndrome) is more slowly progressive and chronic. An acute decrease in cardiac output is often the precipitant.

In addition to discontinuation of diuretics, clinical improvement and an increase in short-term survival may follow one of the following regimens for 7–14 days: (1) intravenous terlipressin (not yet approved by the US FDA, though elsewhere it remains the preferred agent where available) or (2) intravenous norepinephrine plus intravenous albumin 1 g/kg on day 1 followed by 40–50 g/day for the duration of therapy. (3) Oral midodrine plus octreotide, subcutaneously or intravenously, is less effective than terlipressin. Oral midodrine, 7.5 mg three times daily, added to diuretics, increases the blood pressure and has been reported to convert refractory ascites to diuretic-sensitive ascites. (4) Prolongation of survival has been associated with use of MARS (Molecular Adsorbent Recirculating System), a modified dialysis method that selectively removes albumin-bound substances. (5) Improvement in kidney function may follow placement of a TIPS, although data are limited; survival after 1 year is reported to be predicted by the combination of a serum bilirubin level less than 3 mg/dL (50 mcmol/L) and a platelet count greater than 75,000/mcL (75×10^9/L).

Continuous venovenous hemofiltration and hemodialysis are of uncertain value in hepatorenal syndrome. Liver transplantation is the ultimate treatment of choice, but many patients die before a donor liver can be obtained. Mortality correlates with the MELD score and presence of a systemic inflammatory response. AKI-hepatorenal syndrome is often irreversible in patients with a systemic infection. The 3-month probability of survival in cirrhotic patients with hepatorenal syndrome (15%) is lower than that for renal failure associated with infections (31%), hypovolemia (46%), and parenchymal kidney disease (73%).

4. Hepatic encephalopathy—Hepatic encephalopathy is a state of disordered CNS function resulting from failure of the liver to detoxify noxious agents of gut origin because of hepatocellular dysfunction and portosystemic shunting. The clinical spectrum ranges from day-night reversal and mild intellectual impairment to coma. Patients with covert (formerly minimal) hepatic encephalopathy have no recognizable clinical symptoms but demonstrate mild cognitive, psychomotor, and attention deficits on standardized psychometric tests and an increased rate of traffic accidents. The stages of overt encephalopathy are (1) mild confusion, (2) drowsiness, (3) stupor, and (4) coma. A revised staging system known as SONIC (**S**pectrum **O**f **N**eurocognitive **I**mpairment in **C**irrhosis) encompasses absent, covert, and stages 2 to 4 encephalopathy. Ammonia is the most readily identified and measurable toxin but is not solely responsible for the disturbed mental status. Bleeding into the intestinal tract may significantly increase the amount of protein in the bowel and precipitate encephalopathy. Other precipitants include constipation, alkalosis, and potassium deficiency induced by diuretics, opioids, hypnotics, and sedatives; medications containing ammonium or amino compounds; paracentesis with consequent hypovolemia; hepatic or systemic infection; and portosystemic shunts (including TIPS). In one study, risk factors for hepatic encephalopathy in patients with cirrhosis included a higher serum bilirubin level and use of a nonselective beta-blocker, whereas a higher serum albumin level and use of a statin were protective. The diagnosis is based primarily on detection of characteristic symptoms and signs, including asterixis. A smartphone app called EncephalApp using the "Stroop test" (asking the patient to name the color of a written word rather than the word itself, even when the word is the name of a different color) has proved useful for detecting covert hepatic encephalopathy.

Oral protein intake is withheld during acute episodes if the patient cannot eat. When the patient resumes oral intake, protein intake should be 60–80 g/day as tolerated; vegetable protein is better tolerated than meat protein. GI bleeding should be controlled and blood purged from the GI tract. This can be accomplished with 120 mL of magnesium citrate by mouth or nasogastric tube every 3–4 hours until the stool is free of gross blood or by administration of lactulose. The value of treating patients with covert hepatic encephalopathy is uncertain; probiotic agents may have some benefit.

Lactulose, a nonabsorbable synthetic disaccharide syrup, is digested by bacteria in the colon to short-chain fatty acids, resulting in acidification of colon contents. This acidification favors the formation of ammonium ion in the $NH_4^+ \leftrightarrow NH_3 + H^+$ equation; NH_4^+ is not absorbable, whereas NH_3 is absorbable and thought to be neurotoxic. Lactulose also leads to a change in bowel flora so that fewer ammonia-forming organisms are present. When given orally, the initial dose of lactulose for acute hepatic encephalopathy is 30 mL three or four times daily. The dose should then be titrated so that the patient produces 2–3 soft stools per day. When given rectally because the patient is unable to take medicines orally, the dose is 200 g/300 mL given as a solution of lactulose in saline or sorbitol in a retention enema for 30–60 minutes; it may be repeated every 4–6 hours. Bowel cleansing with a polyethylene glycol colonoscopy preparation is also effective in patients with acute overt hepatic encephalopathy and may be preferable. Continued use of lactulose after an

episode of acute encephalopathy reduces the frequency of recurrences.

The ammonia-producing intestinal flora may also be controlled with an oral antibiotic. The nonabsorbable agent rifaximin, 550 mg orally twice daily, is preferred and has been shown as well to maintain remission of and reduce the risk of rehospitalization for hepatic encephalopathy over a 24-month period, with or without the concomitant use of lactulose. Metronidazole, 250 mg orally three times daily, has also shown benefit. Patients who do not respond to lactulose alone may improve with an antibiotic added to treatment with lactulose.

Sodium benzoate, 5 g orally twice daily, ornithine aspartate, 9 g orally three times daily, and L-acyl-carnitine (an essential factor in the mitochondrial transport of long-chain fatty acids), 4 g orally daily, may lower blood ammonia levels, but there is less experience with these drugs than with lactulose. Flumazenil is effective in about 30% of patients with severe hepatic encephalopathy, but the drug is short-acting and intravenous administration is required. Use of special dietary supplements enriched with branched-chain amino acids is usually unnecessary except in occasional patients who are intolerant of standard protein supplements. Opioids and sedatives metabolized or excreted by the liver should be avoided. If agitation is marked, oxazepam, 10–30 mg, which is not metabolized by the liver, may be given cautiously by mouth or by nasogastric tube. Zinc deficiency should be corrected, if present, with oral zinc sulfate, 600 mg/day in divided doses.

5. Coagulopathy—Hypoprothrombinemia caused by malnutrition and vitamin K deficiency may be treated with vitamin K (eg, phytonadione, 5 mg orally or intravenously daily); however, this treatment is ineffective when synthesis of coagulation factors is impaired because of hepatic disease. In such cases, correcting the prolonged prothrombin time would require large volumes of fresh frozen plasma (see Chapter 14). Because the effect is transient, the value of plasma infusions, even for active bleeding or before an invasive procedure, has been questioned because of concomitant alterations in anti-hemostatic factors and because bleeding risk does not correlate with the INR. Recombinant activated factor VIIa may be an alternative but is expensive and poses a 1–2% risk of thrombotic complications. Bleeding risk in critically ill patients with cirrhosis has been shown to correlate with bleeding on hospital admission, a platelet count less than 30,000/mcL (30×10^9/L), a fibrinogen level less than 60 mg/dL (1.764 mcmol/L), and an activated partial thromboplastin time greater than 100 seconds. In patients with active bleeding or undergoing an invasive procedure, goals for management according to some guidelines include a hematocrit value greater than 25%, platelet count greater than 50,000/mcL (50×10^9/L), and fibrinogen level greater than 120 mg/dL (3.528 mcmol/L). A thrombopoietin analog, eg, avatrombopag or lusutrombopag, reduces the need for platelet transfusions in patients with cirrhosis and a platelet count less than 50,000/mcL (50×10^9/L) who undergo invasive procedures but must be administered for at least 3–5 days for the platelet count to start to rise.

6. Hemorrhage from esophageal varices—See Chapter 15.

7. Hepatopulmonary syndrome and portopulmonary hypertension—Shortness of breath in patients with cirrhosis may result from pulmonary restriction and atelectasis caused by massive ascites or hepatic hydrothorax. The hepatopulmonary syndrome—the triad of chronic liver disease, an increased alveolar-arterial gradient while the patient is breathing room air, and intrapulmonary vascular dilatations or arteriovenous communications that result in a right-to-left intrapulmonary shunt—occurs in 5–32% of patients with cirrhosis. Patients often have greater dyspnea (platypnea) and arterial deoxygenation (orthodeoxia) in the upright than in the recumbent position. The diagnosis should be suspected in a cirrhotic patient with a pulse oximetry level of 96% or lower.

Contrast-enhanced echocardiography is a sensitive screening test for detecting pulmonary vascular dilatations, whereas macroaggregated albumin lung perfusion scanning is more specific and may be used to confirm the diagnosis. High-resolution CT may be useful for detecting dilated pulmonary vessels that may be amenable to embolization in patients with severe hypoxemia (PO_2 less than 60 mm Hg [7.8 kPa]) who respond poorly to supplemental oxygen.

Medical therapy has been disappointing. Long-term oxygen therapy is recommended for severely hypoxemic patients. The syndrome may reverse with liver transplantation, although postoperative morbidity and mortality from severe hypoxemic respiratory failure are increased in patients with a preoperative arterial PO_2 less than 44 mm Hg (5.9 kPa) or with substantial intrapulmonary shunting. TIPS may provide palliation in patients with hepatopulmonary syndrome awaiting transplantation.

Portopulmonary hypertension occurs in 0.7% of patients with cirrhosis. Female sex, autoimmune hepatitis, and genetic variation in aromatase have been reported to be risk factors, and large spontaneous portosystemic shunts are present in many affected patients and are associated with a lack of response to treatment. In cases confirmed by right-sided heart catheterization, treatment with the prostaglandins epoprostenol, iloprost, or treprostinil (the latter two are easier to administer); the endothelin-receptor antagonists ambrisentan and macitentan or bosentan (no longer used because of potential hepatotoxicity); the phosphodiesterase-5 inhibitors sildenafil, tadalafil, or vardenafil; the oral prostacyclin receptor agonist selexipag; or the direct cyclic GMP analog riociguat may reduce pulmonary hypertension and thereby facilitate liver transplantation. Beta-blockers worsen exercise capacity and are contraindicated, and calcium channel blockers should be used with caution because they may worsen portal hypertension. Liver transplantation is contraindicated in patients with moderate to severe pulmonary hypertension (mean pulmonary pressure greater than 35 mm Hg).

C. Liver Transplantation

Liver transplantation is indicated in selected cases of irreversible, progressive chronic liver disease, acute-on-chronic

liver failure, acute liver failure, and certain metabolic diseases in which the metabolic defect is in the liver. Absolute contraindications include malignancy (except relatively small hepatocellular carcinomas in a cirrhotic liver—see Chapter 39), advanced cardiopulmonary disease (except hepatopulmonary syndrome), and sepsis. Relative contraindications include age over 70 years, morbid obesity, portal and mesenteric vein thrombosis, active alcohol or drug abuse, severe malnutrition, and lack of patient understanding. With the emergence of effective antiretroviral therapy for HIV disease, a major cause of mortality in these patients has shifted to liver disease caused by HCV and HBV infection; experience to date suggests that the outcome of liver transplantation is comparable to that for non–HIV-infected liver transplant recipients. Patients with alcoholism should generally be abstinent for 6 months. Liver transplantation should be considered in patients with worsening functional status, rising bilirubin, decreasing albumin, worsening coagulopathy, refractory ascites, recurrent variceal bleeding, or worsening encephalopathy; prioritization is based on the MELD (or MELD-Na) score. Treatment of HCV infection should be deferred until after transplantation in patients in whom the MELD score is 21 or higher. Combined liver-kidney transplantation is indicated in patients with associated kidney failure presumed to be irreversible. The major impediment to more widespread use of liver transplantation is a shortage of donor organs. Adult living donor liver transplantation is an option for some patients and extended-criteria donors are used. Five-year survival rates over 80% are now reported. Hepatocellular carcinoma, hepatitis B and C, Budd-Chiari syndrome, and autoimmune liver disease may recur in the transplanted liver. The incidence of recurrence of hepatitis B can be reduced by preoperative and postoperative treatment with a nucleoside or nucleotide analog and perioperative administration of HBIG, and hepatitis C can be treated with direct-acting antiviral agents. Immunosuppression is achieved with combinations of cyclosporine, tacrolimus, sirolimus, corticosteroids, azathioprine, and mycophenolate mofetil and may be complicated by infections, advanced CKD, neurologic disorders, and drug toxicity, as well as graft rejection, vascular occlusion, or bile leaks. Patients taking these drugs are at risk for obesity, diabetes mellitus, and hyperlipidemia and may develop recurrent or de novo NAFLD following transplantation.

Prognosis

The risk of death from compensated cirrhosis is 4.7 times that of the risk in the general population, and the risk from decompensated cirrhosis is 9.7 times higher. Use of statins appears to decrease the risk of decompensation in patients with compensated cirrhosis, in whom the risk of decompensation can be predicted with a scoring system that includes serum albumin, serum bilirubin, age, serum AST and ALT, and platelet count. Prognostic scoring systems for cirrhosis include the Child-Pugh score and MELD score (Table 16–8). The MELD-Na score, which incorporates the serum bilirubin, creatinine, and sodium levels and the INR, is also a measure of mortality risk in patients with end-stage liver disease and is particularly useful for predicting short- and intermediate-term survival and complications of cirrhosis (eg, bacterial peritonitis) as well as determining allocation priorities for donor livers. Additional (MELD-exception) points are given for patients with conditions such as hepatopulmonary syndrome and hepatocellular carcinoma that may benefit from liver transplantation. A MELD score of 17 or more is required for liver transplant listing. In patients with a relatively low MELD score (less than 21) and a low priority for liver transplantation, an elevated hepatic venous pressure gradient, persistent ascites, hepatic encephalopathy, and a low health-related quality of life are additional independent predictors of mortality, and further modifications of the MELD score are under consideration. Only 50% of patients with severe hepatic dysfunction (serum albumin less than 3 g/dL [30 g/L], bilirubin greater than 3 mg/dL [51.3 mcmol/L], ascites, encephalopathy, cachexia, and upper GI bleeding) survive 6 months without transplantation. The risk of death in this subgroup of patients with advanced cirrhosis is associated with muscle wasting, age 65 years or older, mean arterial pressure 82 mm Hg or less, severe kidney dysfunction, cognitive dysfunction, ventilatory insufficiency, prothrombin time 16 seconds or longer, delayed and suboptimal treatment of sepsis, and second infections. For cirrhotic patients admitted to an intensive care unit,

Table 16–8. Child-Pugh and Model for End-Stage Liver Disease (MELD) scoring systems for staging cirrhosis.

Child-Pugh Scoring System			
	Numerical Score		
Parameter	1	2	3
Ascites	None	Slight	Moderate to severe
Encephalopathy	None	Slight to moderate	Moderate to severe
Bilirubin, mg/dL (mcmol/L)	< 2.0 (34.2)	2–3 (34.2–51.3)	> 3.0 (51.3)
Albumin, g/dL (g/L)	> 3.5 (35)	2.8–3.5 (28–35)	< 2.8 (28)
Prothrombin time (seconds increased)	1–3	4–6	> 6.0
	Total Numerical Score and Corresponding Child-Pugh Class		
	Score	Class	
	5–6	A	
	7–9	B	
	10–15	C	
MELD Scoring Systems			
Original MELD score = 11.2 $\log_e$ (INR) + 3.78 $\log_e$ (bilirubin [mg/dL]) + 9.57 $\log_e$ (creatinine [mg/dL]) + 6.43. (Range 6–40.) MELD-Na score = MELD + (140 – Na) × (1 – 0.025 × MELD).			

the Royal Free Hospital score, consisting of the serum bilirubin, INR, serum lactate, alveolar-arterial oxygen gradient, and BUN, has been reported to predict mortality. The combination of the MELD score and serum lactate at the time of hospitalization has been reported to predict inpatient mortality better than the MELD score alone. Severe kidney dysfunction increases mortality up to sevenfold in patients with cirrhosis, and at least 25% of patients who survive an episode of AKI develop CKD. The ratio of neutrophils to lymphocytes in peripheral blood has been reported to correlate with mortality 1 year after a nonelective hospitalization in patients with cirrhosis. Obesity and diabetes mellitus appear to be risk factors for clinical deterioration and cirrhosis-related mortality, as is continued alcohol use in patients with alcohol-associated cirrhosis. The use of beta-blockers for portal hypertension is beneficial early in the course. However, beta-blockers may become ineffective and may be associated with reduced survival in patients with refractory ascites, spontaneous bacterial peritonitis, sepsis, or severe alcohol-associated hepatitis because of their negative effect on cardiac compensatory reserve. In general, beta-blockers should be discontinued when the systolic blood pressure is less than 90 mm Hg, the serum sodium level is less than 130 mEq/L, or AKI has developed, although results of some studies have challenged these guidelines. Patients with cirrhosis are at risk for the development of hepatocellular carcinoma, with rates of 3–5% per year for alcohol-associated and viral hepatitis–related cirrhosis. Liver transplantation has markedly improved the outlook for patients with cirrhosis who are candidates and are referred for evaluation early in the course. Patients with compensated cirrhosis are given additional priority for liver transplantation if they are found to have a lesion larger than 2 cm in diameter consistent with hepatocellular carcinoma. In-hospital mortality from cirrhosis declined from 9.1% in 2002 to 5.4% in 2010 and that from variceal bleeding in patients with cirrhosis declined from over 40% in 1980 to 15% in 2000. Rates and costs of hospital admissions increased substantially between 2005 and 2015, primarily because of increases in the rates of cirrhosis caused by NAFLD. Patients hospitalized with cirrhosis and an infection are at high risk for subsequent infections, particularly if they are older, taking a PPI, or receiving antibiotic prophylaxis for spontaneous bacterial peritonitis.

When to Refer

- For liver biopsy.
- When the MELD score is 14 or higher.
- For upper endoscopy to screen for gastroesophageal varices.

When to Admit

- GI bleeding.
- Stage 3–4 hepatic encephalopathy.
- Worsening kidney function.
- Severe hyponatremia.
- Serious infection.
- Profound hypoxia.

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PRIMARY BILIARY CHOLANGITIS

ESSENTIALS OF DIAGNOSIS

- Occurs in middle-aged women.
- Often asymptomatic.
- Elevation of alkaline phosphatase, positive antimitochondrial antibodies, elevated IgM, increased cholesterol.
- Characteristic liver biopsy.
- In later stages, can present with fatigue, jaundice, features of cirrhosis, xanthelasmas, xanthomas, steatorrhea.

General Considerations

PBC is a chronic disease of the liver characterized by autoimmune destruction of small intrahepatic bile ducts and cholestasis. The designation "primary biliary cholangitis" has replaced "primary biliary cirrhosis" because many patients do not have cirrhosis. The disease is insidious in onset, occurs usually in women aged 40–60 years, and is often detected by the chance finding of elevated alkaline phosphatase levels. Estimated incidence and prevalence rates in the United States are 4.5 and 65.4 per 100,000, respectively, in women, and 0.7 and 12.1 per 100,000, respectively, in men. These rates may be increasing. The frequency of the disease among first-degree relatives of affected persons is 1.3–6%, the risk is increased in second- and third-degree relatives, and the concordance rate in identical twins is high. PBC is associated with HLA *DRB1*08* and *DQB1*. The disease may be associated with Sjögren syndrome, autoimmune thyroid disease, Raynaud syndrome, systemic sclerosis (scleroderma), hypothyroidism, and celiac disease; all patients with PBC should be screened for these conditions. Infection with *Novosphingobium aromaticivorans* or *Chlamydophila pneumoniae* may trigger or cause PBC. A history of UTIs (caused by *E coli* or *Lactobacillus delbrueckii*) and smoking, and possibly use of hormone replacement therapy and hair dye, are risk factors, and clustering of cases in time and space argues for a causative role of environmental agents.

Clinical Findings

A. Symptoms and Signs

Many patients are asymptomatic for years. The onset of clinical illness is insidious and is heralded by fatigue (excessive daytime somnolence) and pruritus. With progression, physical examination reveals hepatosplenomegaly. Xanthomatous lesions may occur in the skin and tendons and around the eyelids. Jaundice, steatorrhea, and signs of portal hypertension are late findings, although occasional patients have esophageal varices despite an early histologic stage. Autonomic dysfunction, including orthostatic hypotension and associated fatigue and cognitive dysfunction, appear to be common. The risk of low bone density, osteoporosis, and fractures is increased in patients with PBC (who tend to be older women) possibly due in part to polymorphisms of the vitamin D receptor.

B. Laboratory Findings

Blood counts are normal early in the disease. Liver biochemical tests reflect cholestasis with elevation of alkaline phosphatase, cholesterol (especially high-density lipoproteins and lipoprotein X), and, in later stages, bilirubin. Antimitochondrial antibodies are present in 95% of patients, and serum IgM levels are elevated.

Diagnosis

The diagnosis of PBC is based on the detection of cholestatic liver chemistries (often initially an isolated elevation of the alkaline phosphatase) and antimitochondrial antibodies in a titer greater than 1:40 in serum. Baseline ultrasonography should be obtained. Liver biopsy is not necessary for diagnosis unless antimitochondrial antibodies are absent but permits histologic staging: I, portal inflammation with granulomas; II, bile duct proliferation, periportal inflammation; III, interlobular fibrous septa; and IV, cirrhosis. Estimations of histologic stage by an "enhanced liver fibrosis (ELF) assay," which incorporates serum levels of hyaluronic acid, tissue inhibitor of metalloproteinase-1, and procollagen III aminopeptide, and by elastography have shown promise.

Differential Diagnosis

The disease must be differentiated from chronic biliary tract obstruction (stone or stricture), carcinoma of the bile ducts, primary sclerosing cholangitis, sarcoidosis, cholestatic drug toxicity (eg, chlorpromazine), and (in some cases) chronic hepatitis. Patients with a clinical and histologic picture of PBC but no antimitochondrial antibodies are said to have antimitochondrial antibody-negative PBC (previously termed "autoimmune cholangitis"), which has been associated with lower serum IgM levels and a greater frequency of smooth muscle antibodies and ANA. Many such patients are found to have antimitochondrial antibodies by immunoblot against recombinant proteins (rather than standard immunofluorescence). Some patients have overlapping features of PBC and autoimmune hepatitis.

Treatment

Cholestyramine (4 g) in water or juice three times daily may be beneficial for pruritus; colestipol and colesevelam may be better tolerated but have not been shown to reduce pruritus. Rifampin, 150–300 mg orally twice daily, is inconsistently beneficial. Opioid antagonists (eg, naloxone, 0.2 mcg/kg/minute by intravenous infusion, or naltrexone, starting at 12.5 mg/day by mouth) show promise in the treatment of pruritus but may cause opioid withdrawal symptoms. The 5-hydroxytryptamine (5-HT_3) serotonin receptor antagonist ondansetron, 4 mg orally three times a day as needed, and the SSRI sertraline, 75–100 mg/day orally, may also provide some benefit. For refractory pruritus, plasmapheresis or extracorporeal albumin dialysis may be needed. Modafinil, 100–200 mg/day orally, may improve daytime somnolence but is poorly tolerated. Deficiencies of vitamins A, D, and K may occur if steatorrhea is present and are aggravated when cholestyramine is administered.

Ursodeoxycholic acid (13–15 mg/kg/day in one or two doses) is the preferred medical treatment for PBC. It has been shown to slow the progression of disease (particularly in early-stage disease), stabilize histology, improve long-term survival, reduce the risk of developing esophageal varices, and delay (and possibly prevent) the need for liver transplantation, even in the absence of liver biochemical improvement. Complete normalization of liver biochemical tests occurs in 20% of treated patients within 2 years and 40% within 5 years, and survival is similar to that of healthy controls when the drug is given to patients with stage 1 or 2 PBC. The rate of improvement in the alkaline phosphatase to normal or near-normal levels has been reported to be lower in men than women (72% vs 80%) and higher in women whose disease is diagnosed after age 70 than before age 30 (90% vs 50%). Ursodeoxycholic acid has also been reported to reduce the risk of recurrent colorectal adenomas in patients with PBC. Side effects include weight gain and rarely loose stools. The drug can be continued during pregnancy.

Obeticholic acid, a farnesoid X receptor agonist, may be added in patients with an incomplete response or intolerance to ursodeoxycholic acid. Obeticholic acid is begun in a dose of 5 mg orally daily and increased to 10 mg daily at 6 months if tolerated, based on the decline in serum alkaline phosphatase and bilirubin levels. In patients with Child-Pugh class B or C cirrhosis, the recommended initial dose was 5 mg weekly; however, the drug can cause serious liver injury in patients with advanced cirrhosis, and its use in these patients has been restricted by the FDA. Treatment with obeticholic acid has been shown to stabilize or reverse hepatic fibrosis. The principal side effect is pruritus. Given the expense of the drug, the cost-effectiveness of obeticholic acid has been questioned.

Bezafibrate (not available in the United States) and fenofibrate, which activate peroxisome proliferator–activated receptors (PPARs) and inhibit bile acid synthesis, have shown promise as second-line agents and improve symptoms (including pruritus), liver biochemical test levels, and fibrosis. Colchicine (0.6 mg orally twice daily) and methotrexate (15 mg/wk orally) have had some reported benefit in improving symptoms and serum levels of

alkaline phosphatase and bilirubin. Methotrexate may also improve liver histology in some patients, but overall response rates have been disappointing. For patients with advanced disease, liver transplantation is the treatment of choice.

Prognosis

Without liver transplantation, survival averages 7–10 years once symptoms develop but has improved for younger women since the introduction of ursodeoxycholic acid. Progression to liver failure and portal hypertension may be accelerated by smoking; outcomes are worse in men than in women. Patients with early-stage disease in whom the alkaline phosphatase and AST are less than 1.5 times normal and bilirubin is 1 mg/dL (17.1 mcmol/L) or less after 1 year of therapy with ursodeoxycholic acid (Paris II criteria) are at low long-term risk for cirrhosis and have a life expectancy similar to that of the healthy population. Attainment of a serum bilirubin level less than 0.6 times the upper limit of normal or a normal alkaline phosphatase level is associated with the lowest risk for liver transplantation or death. Pregnancy is well tolerated in younger patients. In advanced disease, an adverse prognosis is indicated by a high Mayo risk score that includes older age, high serum bilirubin, edema, low serum albumin, and prolonged prothrombin time as well as by variceal hemorrhage. Other prognostic models include the Globe index, which is based on age, serum bilirubin, serum albumin, serum alkaline phosphatase, and platelet count and, in treated patients, the UK-PBC score, which is based on the baseline serum albumin and platelet count and the serum bilirubin, aminotransferases, and alkaline phosphatase after 12 months of ursodeoxycholic acid. An increase in liver stiffness of more than 2.1 kPa per year indicates an adverse prognosis. A prediction tool for varices has been proposed based on the serum albumin, serum alkaline phosphatase, platelet count, and splenomegaly. Fatigue is associated with an increased risk of cardiac mortality and may not be reversed by liver transplantation. Among asymptomatic patients, a decline in liver function is observed in up to 50% by 5 years, and at least one-third will become symptomatic within 15 years. The risk of hepatocellular carcinoma appears to be increased in patients with PBC; risk factors include older age, male sex, prior blood transfusions, advanced histologic stage, signs of cirrhosis or portal hypertension, and a biochemical nonresponse to ursodeoxycholic acid. Liver transplantation should be considered when the MELD-Na score is at least 15, total serum bilirubin at least 6, or Mayo risk score at least 7.8. Liver transplantation for advanced PBC is associated with a 1-year survival rate of 85–90%. The disease recurs in the graft in 20% of patients by 3 years and 37% by 10 years. A reduced risk of recurrence, graft loss, and death is associated with preventive treatment with ursodeoxycholic acid in combination with cyclosporine (rather than tacrolimus).

When to Refer

- For liver biopsy.
- For liver transplant evaluation.

When to Admit

- GI bleeding.
- Stage 3–4 hepatic encephalopathy.
- Worsening kidney function.
- Severe hyponatremia.
- Profound hypoxia.

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HEMOCHROMATOSIS

ESSENTIALS OF DIAGNOSIS

- Usually suspected because of a family history or an elevated iron saturation or serum ferritin.
- Most patients are asymptomatic; the disease is rarely recognized clinically before the fifth decade.
- Hepatic abnormalities and cirrhosis, heart failure, hypogonadism, and arthritis.
- *HFE* gene mutation (usually C282Y/C282Y) is found in most cases.

General Considerations

Hemochromatosis is an autosomal recessive disease caused in most cases by a pathogenic variant in the *HFE* gene on chromosome 6. The HFE protein is thought to play an important role in the process by which duodenal crypt cells sense body iron stores, and the variant gene leads to increased iron absorption from the duodenum. A decrease in the synthesis or expression of hepcidin, the principal iron regulatory hormone, is thought to be a key pathogenic factor in all forms of hemochromatosis. About 85% of persons with well-established hemochromatosis are homozygous for the C282Y variant (type 1a hemochromatosis). The frequency of the C282Y variant averages 7% in Northern European and North American White populations, resulting in a 0.5% frequency of homozygotes (of whom 38–50% will develop biochemical evidence of iron overload but only 28% of men and 1% of women will develop clinical symptoms). The C282Y gene variant and

hemochromatosis are uncommon in Black and Asian American populations. A second genetic variant (H63D) may contribute to the development of iron overload in a small percentage (1.5%) of persons who are compound heterozygotes for C282Y and H63D (type 1b); iron overload–related disease develops in only a few patients (particularly those who have a comorbidity such as diabetes mellitus and fatty liver). A third gene variant (S65C) may lead to increased serum iron and ferritin levels without clinical significance (type 1c). High serum ferritin levels are seen in hyperferritinemia cataract syndrome associated with pathogenic variants in the *FTL* (ferritin L-chain) gene. An uncommon juvenile-onset variant that is characterized by severe iron overload, cardiac dysfunction, hypogonadotropic hypogonadism, and a high mortality rate is usually linked to a variant gene on chromosome 1q designated *HJV* that produces a protein called hemojuvelin (type 2a) or, rarely, to a variant of the *HAMP* gene on chromosome 19 that encodes hepcidin (type 2b). Rare instances of hemochromatosis result from pathogenic variants in the genes that encode transferrin receptor 2 (*TFR2*) (type 3) and ferroportin (*SLC40A1*) (type 4a). Type 4b hemochromatosis is characterized by resistance of ferroportin to hepcidin.

Hemochromatosis is characterized by increased accumulation of iron as hemosiderin in the liver, pancreas, heart, adrenals, testes, pituitary, and kidneys. Cirrhosis is more likely to develop in affected persons who drink alcohol excessively or have obesity-related hepatic steatosis than in those who do not; other risk factors include age and diabetes mellitus. Eventually, hepatic and pancreatic insufficiency, heart failure, and hypogonadism may develop. Heterozygotes do not develop cirrhosis in the absence of associated disorders such as viral hepatitis or NAFLD.

Clinical Findings

A. Symptoms and Signs

The onset of clinical disease is usually after age 50 years—earlier in men than in women; however, because of widespread liver biochemical testing and iron screening, the diagnosis is usually made long before symptoms develop. Early symptoms are nonspecific (eg, fatigue, arthralgia). Later clinical manifestations include a symmetric arthropathy that is similar to osteoarthritis and calcium pyrophosphate deposition disease (and ultimately the need for joint replacement surgery in some cases), hepatomegaly and evidence of hepatic dysfunction, skin pigmentation (combination of slate-gray due to iron and brown due to melanin, sometimes resulting in a bronze color), cardiac enlargement with or without heart failure or conduction defects, diabetes mellitus with its complications, and erectile dysfunction in men. Interestingly, population studies have shown an increased prevalence of liver disease but not of diabetes mellitus, arthritis, or heart disease in C282Y homozygotes. In patients in whom cirrhosis develops, bleeding from esophageal varices may occur, and there is a 15–20% frequency of hepatocellular carcinoma; the risk of intrahepatic cholangiocarcinoma is also increased. Affected patients are at increased risk of infection with *Vibrio vulnificus, Listeria monocytogenes, Yersinia enterocolitica*, and other siderophilic organisms. The risk of porphyria cutanea tarda is increased in persons with the C282Y or H63D variants, and C282Y homozygotes have twice the risk of colorectal and breast cancer than persons without the C282Y variant.

B. Laboratory Findings

Laboratory findings include mildly abnormal liver tests (AST, alkaline phosphatase), an elevated plasma iron with greater than 45% transferrin saturation, a low unsaturated iron-binding capacity, and an elevated serum ferritin (although a normal iron saturation or a normal ferritin does not exclude the diagnosis). Affected men are more likely than affected women to have an elevated ferritin level. Testing for *HFE* variants is indicated in any patient with evidence of iron overload. Interestingly, in persons with an elevated serum ferritin, the likelihood of detecting C282Y homozygosity decreases with increasing ALT and AST levels, which likely reflect hepatic inflammation and secondary iron overload. In contrast to secondary iron overload, the serum ALT level is often normal.

C. Imaging

MRI and CT may show changes consistent with iron overload of the liver, and MRI-based techniques (eg, T2 spin echo and T2* gradient-recalled echo MRI) can quantitate hepatic iron stores and help assess the degree of hepatic fibrosis.

D. Liver Biopsy

In patients who are homozygous for C282Y, liver biopsy is often indicated to determine whether cirrhosis is present. Biopsy can be deferred, however, in patients in whom the serum ferritin level is less than 1000 mcg/L, serum AST level is normal, and hepatomegaly is absent; the likelihood of cirrhosis is low in these persons. Serum biomarkers of fibrosis may be an alternative to liver biopsy for identifying advanced fibrosis. Risk factors for advanced fibrosis include male sex, excess alcohol consumption, and diabetes mellitus. Liver biopsy also may be indicated when iron overload is suspected even though the patient is neither homozygous for C282Y nor a C282Y/H63D compound heterozygote. In patients with hemochromatosis, the liver biopsy characteristically shows extensive iron deposition in hepatocytes and in bile ducts, and the hepatic iron index—hepatic iron content per gram of liver converted to micromoles and divided by the patient's age—is generally higher than 1.9 (though no longer used for diagnosis). Only 5% of patients with hereditary hemochromatosis identified by screening in a primary care setting have cirrhosis.

Screening

Iron studies and *HFE* testing are recommended for all first-degree family members of a proband; children of an affected person (C282Y homozygote) need to be screened only if the patient's spouse carries the C282Y or H63D mutation. General population screening for

hemochromatosis is not recommended because the clinical penetrance of C282Y homozygosity and morbidity and mortality from hemochromatosis are low. Patients with otherwise unexplained chronic liver disease, chondrocalcinosis, erectile dysfunction, and type 1 diabetes mellitus (especially late-onset) should be screened for iron overload.

Treatment

Affected persons are advised to avoid foods rich in iron (such as red meat), alcohol, vitamin C, raw shellfish, and supplemental iron, although dietary restrictions may not be necessary in those undergoing phlebotomy. Weekly phlebotomies of 1 or 2 units (250–500 mL) of blood (each containing about 250 mg of iron) are indicated in all symptomatic patients, and those with a serum ferritin level of at least 300 mcg/L (men) or 200 mcg/L (women) with an increased fasting iron saturation (greater than or equal to 45%); these phlebotomies should be continued for up to 2–3 years to achieve depletion of iron stores. The hematocrit and serum iron values should be monitored. When iron store depletion is achieved (iron saturation less than 50% and serum ferritin level 50–100 mcg/L), phlebotomies (every 2–4 months) to maintain serum ferritin levels between 50 mcg/L and 100 mcg/L are continued, although compliance has been reported to decrease with time. Administration of a PPI, which reduces intestinal iron absorption, decreases the maintenance phlebotomy volume requirement. In C282Y homozygous women, a BMI greater than 28 is associated with a lower phlebotomy requirement, possibly because hepcidin levels are increased by overweight. Complications of hemochromatosis—arthropathy, diabetes mellitus, heart disease, portal hypertension, and hypopituitarism—also require treatment.

The chelating agent deferoxamine is indicated for patients with hemochromatosis and anemia or in those with secondary iron overload due to thalassemia who cannot tolerate phlebotomies. The drug is administered intravenously or subcutaneously in a dosage of 20–40 mg/kg/day infused over 24 hours and can mobilize 30 mg of iron per day; however, treatment is painful and time-consuming. Two oral chelators, deferasirox, 20 mg/kg once daily, and deferiprone, 25 mg/kg three times daily, have been approved for treatment of iron overload due to blood transfusions and may be appropriate in persons with hemochromatosis who cannot tolerate phlebotomy; however, these agents have a number of side effects and drug-drug interactions.

The course of hemochromatosis appears to be favorably altered by phlebotomy therapy, although the evidence for a benefit is surprisingly sparse. With phlebotomy therapy, hepatic fibrosis may regress, and in precirrhotic patients, cirrhosis may be prevented. Cardiac conduction defects may improve with treatment. Joint disease, diabetes mellitus, and hypogonadism may not reverse with treatment of hemochromatosis. More severe joint symptoms are associated with persistent increases in the transferrin saturation, even if the serum ferritin level is maintained below 50 mcg/L. In patients with cirrhosis, varices may reverse, the risk of variceal bleeding declines, and the risk of hepatocellular carcinoma may be reduced. In those with an initial serum ferritin level greater than 1000 mcg/L (2247 pmol/L), the risk of death is fivefold greater than in those with a serum ferritin of 1000 mcg/L (2247 pmol/L) or less. In treated patients, only those with a serum ferritin greater than 2000 mcg/L (4494 pmol/L) are reported to have increased mortality, mainly related to liver disease. Since 1997, posttransplant survival rates have been excellent. Following liver transplantation, serum iron studies and hepcidin levels are normal, and phlebotomy is not required.

When to Refer

- For liver biopsy.
- For initiation of therapy.

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WILSON DISEASE

ESSENTIALS OF DIAGNOSIS

- Rare autosomal recessive disorder that usually occurs in persons under age 40.
- Excessive deposition of copper in the liver and brain.
- Serum ceruloplasmin, the plasma copper-carrying protein, is low.
- Urinary excretion of copper and hepatic copper concentration are high.

General Considerations

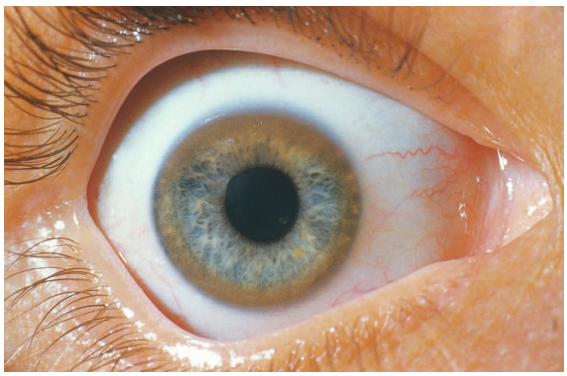
Wilson disease (hepatolenticular degeneration) is a rare autosomal recessive disorder that usually occurs in persons between 3 and 55 years of age. The worldwide prevalence is generally stated to be about 30 per million population, but the frequency of the allele appears to be greater than implied by this estimate. The condition is characterized by excessive deposition of copper in the liver and brain. The genetic defect, localized to chromosome 13 (*ATP7B*), has been shown to affect a copper-transporting adenosine triphosphatase in the liver and leads to copper accumulation in the liver and oxidative damage of hepatic mitochondria. Most patients are compound heterozygotes (ie, carry two different pathogenic variants). Over 600 variants in the Wilson disease gene have been identified. The H1069Q variant accounts for

37–63% of disease alleles in populations of Northern European descent. The major physiologic aberration in Wilson disease is excessive absorption of copper from the small intestine and decreased excretion of copper by the liver, resulting in increased tissue deposition, especially in the liver, brain, cornea, and kidney.

Clinical Findings

Wilson disease tends to present as liver disease in adolescents (more common in females) and neuropsychiatric disease in young adults (more common in males), but there is great variability, and onset of symptoms after age 40 is more common than previously thought. The diagnosis should always be considered in any child or young adult with hepatitis, splenomegaly with hypersplenism, Coombs-negative hemolytic anemia, portal hypertension, and neurologic or psychiatric abnormalities. Wilson disease should also be considered in persons under 40 years of age with chronic hepatitis or acute liver failure.

Hepatic involvement may range from elevated liver biochemical tests (although the alkaline phosphatase may be low, particularly in patients with acute severe liver disease) to cirrhosis and portal hypertension. In patients with acute liver failure (seen more often in women than in men), the diagnosis of Wilson disease is suggested by an alkaline phosphatase (in U/L)-to-total bilirubin (in mg/dL) ratio less than 4 and an AST-to-ALT ratio greater than 2.2. The neurologic manifestations of Wilson disease are related to basal ganglia dysfunction and include an akinetic-rigid syndrome similar to parkinsonism, pseudosclerosis with tremor, ataxia, and a dystonic syndrome. Dysarthria, dysphagia, incoordination, and spasticity are common. Migraines, insomnia, and seizures have been reported. Psychiatric features include behavioral and personality changes and emotional lability and may precede characteristic neurologic features. The risk of depression is increased. The pathognomonic sign of the condition is the brownish or gray-green Kayser-Fleischer ring, which represents fine pigmented granular deposits in Descemet membrane in the cornea (Figure 16–4). The ring is usually most marked at the superior and inferior poles of the cornea. It is sometimes seen with the naked eye and is readily detected by slit-lamp examination. It may be absent in patients with hepatic manifestations only but is usually present in those with neuropsychiatric disease. Renal calculi, aminoaciduria, renal tubular acidosis, hypoparathyroidism, infertility, hemolytic anemia, and subcutaneous lipomas may occur.



▲ **Figure 16–4. Brownish Kayser-Fleischer ring at the rim of the cornea in a patient with Wilson disease.** (Used, with permission, from Mediscan/Alamy Stock Photo.)

Diagnosis

The diagnosis can be challenging, even with the use of scoring systems (eg, the Leipzig criteria), and is generally based on demonstration of increased urinary copper excretion (greater than 40 mcg/24 hours and usually greater than 100 mcg/24 hours) or low serum ceruloplasmin levels (less than 14 mg/dL [140 mg/L]; less than 10 mg/dL [100 mg/L] strongly suggests the diagnosis), and elevated hepatic copper concentration (greater than 250 mcg/g of dry liver) as well as Kayser-Fleischer rings, neurologic symptoms, and Coombs-negative hemolytic anemia. However, increased urinary copper (on three separate 24-hour collections) and a low serum ceruloplasmin level (by a standard immunologic assay), while useful, are neither completely sensitive nor specific for Wilson disease, although an enzymatic assay for ceruloplasmin appears to be more accurate and more sensitive for screening than urinary copper excretion; lipemia can interfere with the measurement of ceruloplasmin by the standard assay. The ratio of exchangeable copper to total copper in serum has been reported to be a reliable test for the diagnosis of Wilson disease. Liver biopsy may show acute or chronic hepatitis or cirrhosis. MRI of the brain may show evidence of increased basal ganglia, brainstem, and cerebellar copper even early in the course of the disease. If available, molecular analysis of *ATP7B* pathogenic variants can be diagnostic.

Treatment

Early treatment to remove excess copper before it can produce hepatic or neurologic damage is essential. Initially, restriction of dietary copper (shellfish, organ foods, nuts, mushrooms, and chocolate) may be of value. Oral D-penicillamine (0.75–2 g/day in divided doses taken 1 hour before or 2 hours after food) has traditionally been the drug of choice and enhances urinary excretion of chelated copper. Oral pyridoxine, 50 mg per week, is added because D-penicillamine is an antimetabolite of this vitamin. If D-penicillamine treatment cannot be tolerated because of GI intolerance, hypersensitivity, autoimmune reactions, nephrotoxicity, or bone marrow toxicity, trientine hydrochloride, 250–500 mg three times a day, a chelating agent as effective as D-penicillamine but with a lower rate of adverse effects, is used and is increasingly prescribed as a first-line agent, although its cost has become exorbitant. Oral zinc acetate or zinc gluconate, 50 mg of elemental zinc three times a day taken 30 minutes before or 2 hours after a meal, interferes with intestinal absorption of copper, promotes fecal copper excretion, and has been used as first-line therapy in asymptomatic or pregnant patients and those with neurologic disease, in

combination with a chelating agent, or as maintenance therapy after decoppering with a chelating agent, but adverse GI effects often lead to discontinuation and its long-term efficacy and safety (including a risk of hepatotoxicity) have been questioned; it can lead to copper deficiency in normal persons.

Treatment should continue indefinitely. The doses of penicillamine and trientine should be reduced during pregnancy. Supplemental vitamin E, an antioxidant, has been recommended but not rigorously studied. Once the serum nonceruloplasmin copper level is within the normal range (50–150 mcg/L), the dose of chelating agent can be reduced to the minimum necessary for maintaining that level. The prognosis is good in patients who are effectively treated before liver or brain damage has occurred, but long-term survival is reduced in patients with cirrhosis at diagnosis (84% after 20 years). Liver transplantation is indicated for acute liver failure (often after plasma exchange or dialysis with MARS as a stabilizing measure) and decompensated cirrhosis (with excellent outcomes). Liver transplantation is generally not recommended for intractable isolated neuropsychiatric disease. All first-degree relatives, especially siblings, require screening with serum ceruloplasmin, liver biochemical tests, and slit-lamp examination or, if the causative pathogenic gene variant is known, with variant analysis.

When to Refer

All patients with Wilson disease should be referred for diagnosis and treatment.

When to Admit

- Acute liver failure.
- GI bleeding.
- Stage 3–4 hepatic encephalopathy.
- Worsening kidney function.
- Severe hyponatremia.
- Profound hypoxia.

Collins CJ et al. Direct measurement of ATP7B peptides is highly effective in the diagnosis of Wilson disease. Gastroenterology. 2021;160:2367. [PMID: 33640437]

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HEPATIC VENOUS OUTFLOW OBSTRUCTION (Budd-Chiari Syndrome)

ESSENTIALS OF DIAGNOSIS

- Right upper quadrant pain and tenderness.
- Ascites.
- Imaging studies show occlusion/absence of flow in the hepatic vein(s) or inferior vena cava.
- Clinical picture is similar in sinusoidal obstruction syndrome, but major hepatic veins are patent.

General Considerations

Factors that predispose patients to hepatic venous outflow obstruction, or Budd-Chiari syndrome, including hereditary and acquired hypercoagulable states, can be identified in up to 85% of affected patients; multiple disorders are found in up to 45%. Up to 50% of cases are associated with polycythemia vera or other myeloproliferative neoplasms (which entail a 1% risk of Budd-Chiari syndrome). These cases are often associated with a specific pathogenic variant (*V617F*) in the gene that codes for JAK2 tyrosine kinase and may otherwise be subclinical. Other predispositions to thrombosis (eg, activated protein C resistance [factor V Leiden mutation] [25% of cases], protein C or S or antithrombin deficiency [23%], antiphospholipid antibodies [20%], hyperprothrombinemia [factor II *G20210A* pathogenic variant] [rarely], the methylenetetrahydrofolate reductase *TT677* variant) may be identified in other cases. Hepatic vein obstruction may be associated with caval webs, right-sided heart failure or constrictive pericarditis, neoplasms that cause hepatic vein occlusion, paroxysmal nocturnal hemoglobinuria, hyperhomocysteinemia, Behçet syndrome, vasculitis, sarcoidosis, IBD, celiac disease, blunt abdominal trauma, use of oral contraceptives, and pregnancy. In India, China, and South Africa, Budd-Chiari syndrome is associated with a poor standard of living and often the result of occlusion of the hepatic portion of the inferior vena cava, presumably due to prior thrombosis. The clinical presentation is mild, but the course is frequently complicated by hepatocellular carcinoma.

Some cytotoxic agents and pyrrolizidine alkaloids (comfrey or "bush teas") may cause **sinusoidal obstruction syndrome** (previously known as veno-occlusive disease because the terminal venules are often occluded), which mimics Budd-Chiari syndrome clinically. Sinusoidal obstruction syndrome may occur in patients who have undergone hematopoietic stem cell transplantation, particularly those with pretransplant serum aminotransferase elevations or fever during cytoreductive therapy with cyclophosphamide, azathioprine, carmustine, busulfan, etoposide, or gemtuzumab ozogamicin or those receiving high-dose cytoreductive therapy or high-dose total body irradiation.

Clinical Findings

A. Symptoms and Signs

The presentation is most commonly subacute but may be fulminant, acute, or chronic; it may present as acute-on-chronic liver failure (see Cirrhosis). Clinical manifestations generally include ascites, painful hepatic enlargement, jaundice, splenomegaly, and AKI. With chronic disease, bleeding varices and hepatic encephalopathy may be evident; hepatopulmonary syndrome may occur.

B. Imaging

Hepatic imaging studies may show a prominent caudate lobe since its venous drainage may be occluded. The screening test of choice is contrast-enhanced, color, or pulsed-Doppler ultrasonography, which has a sensitivity of 85% for detecting evidence of hepatic venous or inferior vena caval thrombosis. MRI with spin-echo and gradient-echo sequences and intravenous gadolinium injection allows visualization of the obstructed veins and collateral vessels. Direct venography can delineate caval webs and occluded hepatic veins ("spider-web" pattern) most precisely but is rarely required. Concomitant splanchnic vein thrombosis may be found in 4–21% of cases.

C. Liver Biopsy

Percutaneous or transjugular liver biopsy in Budd-Chiari syndrome may be considered when the results of noninvasive imaging are inconclusive and frequently shows characteristic centrilobular congestion and fibrosis and often multiple large regenerative nodules. Liver biopsy is rarely required, however, and is often contraindicated in sinusoidal obstruction syndrome because of thrombocytopenia, and the diagnosis is based on clinical findings.

Treatment

Ascites should be treated with salt restriction and diuretics. Treatable causes of Budd-Chiari syndrome should be sought. Prompt recognition and treatment of an underlying hematologic disorder may avoid the need for surgery; however, the optimal anticoagulation regimen is uncertain, and anticoagulation is associated with a high risk of bleeding, particularly in patients with portal hypertension and those undergoing invasive procedures. Low-molecular-weight heparins are preferred over unfractionated heparin because of a high rate of heparin-induced thrombocytopenia with the latter. Warfarin is also an acceptable treatment, and direct-acting oral anticoagulants seem to have comparable efficacy but lack a reversal agent. Infusion of a thrombolytic agent into recently occluded veins has been attempted with success. Defibrotide, an adenosine receptor agonist that increases endogenous tissue plasminogen activator levels, has been approved by the FDA for the prevention and treatment of the sinusoidal obstruction syndrome. The drug is given as an intravenous infusion every 6 hours for a minimum of 21 days. Serious adverse effects include hypotension and hemorrhage; the drug is expensive and has no benefit in severe sinusoidal obstruction syndrome.

Balloon angioplasty, often with placement of an intravascular metallic stent, is preferred in patients with an inferior vena caval web and is being performed commonly in patients with hepatic vein thrombosis. TIPS placement may be attempted in patients with Budd-Chiari syndrome and persistent hepatic congestion or failed thrombolytic therapy and possibly in those with sinusoidal obstruction syndrome. Late TIPS dysfunction is less frequent with the use of polytetrafluoroethylene-covered stents than uncovered stents. TIPS is preferred over surgical decompression (side-to-side portacaval, mesocaval, or mesoatrial shunt), which, in contrast to TIPS, has generally not been proven to improve long-term survival. Older age, a higher serum bilirubin level, and a greater INR predict a poor outcome with TIPS. When TIPS is technically not feasible because of complete hepatic vein obstruction, ultrasound-guided direct intrahepatic portosystemic shunt is an alternative approach. Liver transplantation can be considered in patients with acute liver failure, cirrhosis with hepatocellular dysfunction, and failure of a portosystemic shunt, and outcomes have improved with the advent of patient selection based on the MELD score. Patients with Budd-Chiari syndrome often require lifelong anticoagulation and treatment of the underlying myeloproliferative disease; antiplatelet therapy with aspirin and hydroxyurea has been suggested as an alternative to warfarin in patients with a myeloproliferative disorder. For all patients with Budd-Chiari syndrome, a poor outcome has been reported to correlate with Child-Pugh class C and a lack of response to interventional therapy of any kind.

Prognosis

The overall 5-year survival rate is 50–90% with treatment (but less than 10% without intervention). Adverse prognostic factors in patients with Budd-Chiari syndrome are older age, high Child-Pugh score, ascites, encephalopathy, sepsis, elevated total bilirubin, prolonged prothrombin time, elevated serum creatinine, acute respiratory failure, concomitant portal vein thrombosis, cancer, and histologic features of acute liver disease superimposed on chronic liver injury. The 3-month mortality may be predicted by the Rotterdam score, which is based on encephalopathy, ascites, prothrombin time, and bilirubin. A serum ALT level at least fivefold above the upper limit of normal on presentation indicates hepatic ischemia and predicts a poor outcome, particularly when the ALT level decreases slowly. The risk of hepatocellular carcinoma is increased, and patients with chronic Budd-Chiari syndrome should undergo surveillance with abdominal ultrasonography and serum alpha-fetoprotein levels every 6 months; risk factors include cirrhosis, combined hepatic vein and inferior vena cava obstruction, and a long-segment inferior vena cava block.

When to Admit

All patients with hepatic vein obstruction should be hospitalized.

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Sharma A et al. An update on the management of Budd-Chiari syndrome. Dig Dis Sci. 2021;66:1780. [PMID: 32691382]

Simonetto DA et al. ACG Clinical Guideline: disorders of the hepatic and mesenteric circulation. Am J Gastroenterol. 2020;115:18. [PMID: 31895720]

Thuluvath PJ et al. A scoring model to predict in-hospital mortality in patients with Budd-Chiari syndrome. Am J Gastroenterol. 2021;116:1905. [PMID: 33900212]

THE LIVER IN HEART FAILURE

Ischemic hepatitis, also called **ischemic hepatopathy, hypoxic hepatitis, shock liver**, or **acute cardiogenic liver injury**, may affect 2.5 of every 100 patients admitted to an ICU and results from an acute fall in cardiac output due to acute MI, arrhythmia, or septic or hemorrhagic shock, usually in a patient with passive congestion of the liver. Rare cases have occurred in patients with COVID-19. Clinical hypotension may be absent (or unwitnessed). In some cases, the precipitating event is arterial hypoxemia due to respiratory failure, sleep apnea, severe anemia, heat stroke, carbon monoxide poisoning, cocaine use, or bacterial endocarditis. More than one precipitant is common. Statin therapy prior to admission may protect against ischemic hepatitis.

The hallmark of ischemic hepatitis is a rapid and striking elevation of serum aminotransferase levels (often greater than 5000 U/L); an early rapid rise in the serum LD level (with an ALT-to-LD ratio less than 1.5) is also typical. Elevations of serum alkaline phosphatase and bilirubin are usually mild, but jaundice is associated with worse outcomes. The prothrombin time may be prolonged, and encephalopathy or hepatopulmonary syndrome may develop. The mortality rate due to the underlying disease is high (particularly in patients receiving vasopressor therapy or with septic shock, acute kidney disease, or coagulopathy), but in patients who recover, the aminotransferase levels return to normal quickly, usually within 1 week—in contrast to viral hepatitis.

In patients with **passive congestion of the liver** ("nutmeg liver") due to right-sided heart failure, the serum bilirubin level may be elevated, occasionally as high as 40 mg/dL (684 mcmol/L), due in part to hypoxia of perivenular hepatocytes, and its level is a predictor of mortality and morbidity. Serum alkaline phosphatase levels are normal or slightly elevated, and, in the absence of superimposed ischemia, aminotransferase levels are only mildly elevated. Hepatojugular reflux is present, and with tricuspid regurgitation the liver may be pulsatile. Ascites may be out of proportion to peripheral edema, with a high serum ascites-albumin gradient (greater than or equal to 1.1) and an ascitic fluid protein level of more than 2.5 g/dL (25 g/L). A markedly elevated serum N-terminal-proBNP or BNP level (greater than 364 pg/mL [364 ng/L]) has been reported to distinguish ascites due to heart failure from ascites due to cirrhosis in the absence of renal insufficiency. In severe cases, signs of encephalopathy may develop. Liver stiffness measurement by elastography is increased even in the absence of fibrosis. Mortality is generally attributable to the underlying heart disease but has also been reported to correlate with a noninvasive measure of liver stiffness. The MELD score excluding the INR (MELD-XI) predicts the clinical outcome.

Breu AC et al. A multicenter study into causes of severe acute liver injury. Clin Gastroenterol Hepatol. 2019;17:1201. [PMID: 30103039]

Fortea JI et al. Congestive hepatopathy. Int J Mol Sci. 2020;21:9420. [PMID: 33321947]

Horvatits T et al. Liver injury and failure in critical illness. Hepatology. 2019;70:2204. [PMID: 31215660]

NONCIRRHOTIC PORTAL HYPERTENSION

ESSENTIALS OF DIAGNOSIS

- Splenomegaly or upper GI bleeding from esophageal or gastric varices in patients without liver disease.
- Portal vein thrombosis complicating cirrhosis.

General Considerations

Causes of noncirrhotic portal hypertension include extrahepatic portal vein obstruction (portal vein thrombosis often with cavernous transformation [portal cavernoma]), splenic vein obstruction (presenting as gastric varices without esophageal varices), schistosomiasis, nodular regenerative hyperplasia, and arterial-portal vein fistula. Idiopathic noncirrhotic portal hypertension is common in India and has been attributed to chronic infections, exposure to medications or toxins, prothrombotic disorders, immunologic disorders, and genetic disorders that result in obliterative vascular lesions in the liver. It is rare in Western countries, where increased mortality is attributable to associated disorders and older age; the term portosinusoidal vascular disease has been proposed.

Portal vein thrombosis may occur in 10–25% of patients with cirrhosis, is associated with the severity of the liver disease and related in part to acquired protein C deficiency and splenorenal shunts (resulting in stagnant portal venous blood flow), and may be associated with hepatocellular carcinoma and possibly clinical deterioration but not with increased mortality. Other risk factors for portal vein thrombosis are oral contraceptive use, pregnancy, chronic inflammatory diseases (including pancreatitis), injury to the portal venous system (including surgery), other malignancies, and treatment of thrombocytopenia with eltrombopag. Portal vein thrombosis may be classified as type 1, involving the main portal vein; type 2, involving one (2a) or both (2b) branches of the portal vein; or type 3, involving the trunk and branches of the portal vein. Additional descriptors are occlusive or nonocclusive, recent or chronic, and extension (into the mesenteric vein) as well as the nature of any underlying liver disease. Splenic vein thrombosis may complicate pancreatitis or pancreatic cancer. Pylephlebitis (septic thrombophlebitis of the portal vein) may complicate intra-abdominal inflammatory disorders such as appendicitis or diverticulitis, particularly when anaerobic organisms (especially *Bacteroides* species) are involved. Nodular regenerative hyperplasia results from altered hepatic perfusion and can be associated with collagen vascular diseases; myeloproliferative disorders; and drugs, including azathioprine, 5-fluorouracil, oxaliplatin, and thioguanine. In patients infected with HIV, long-term use of didanosine and use of a combination of didanosine and stavudine have been reported to account for some cases of noncirrhotic portal hypertension often due to nodular regenerative hyperplasia; genetic factors may play a role. The term "obliterative portal

venopathy" is used to describe primary occlusion of intrahepatic portal veins in the absence of cirrhosis, inflammation, or hepatic neoplasia.

Clinical Findings

A. Symptoms and Signs

Acute portal vein thrombosis usually causes abdominal pain. Aside from splenomegaly, the physical findings are not remarkable, although hepatic decompensation can follow severe GI bleeding, and intestinal infarction may occur when portal vein thrombosis is associated with mesenteric venous thrombosis. Ascites may occur in 25% of persons with noncirrhotic portal hypertension. Covert hepatic encephalopathy is reported to be common in patients with noncirrhotic portal vein thrombosis.

B. Laboratory Findings

Liver biochemical test levels are usually normal, but there may be findings of hypersplenism. An underlying hypercoagulable state is found in many noncirrhotic patients with portal vein thrombosis in the absence of an obvious provoking factor; this includes myeloproliferative neoplasms (often associated with a specific pathogenic variant [*V617F*] in the gene coding for JAK2 tyrosine kinase, which is found in 24% of cases of portal vein thrombosis), pathogeni variant *G20210A* of prothrombin, factor V Leiden variant, protein C and S deficiency, antiphospholipid syndrome, pathogenic variant *TT677* of methylenetetrahydrofolate reductase, elevated factor VIII levels, hyperhomocysteinemia, and a variant of the gene that codes for thrombin-activatable fibrinolysis inhibitor. It is possible, however, that in many cases evidence of hypercoagulability is a secondary phenomenon due to portosystemic shunting and reduced hepatic blood flow.

C. Imaging

Color Doppler ultrasonography is usually the initial diagnostic test for portal vein thrombosis. Contrast-enhanced CT or magnetic resonance angiography (MRA) of the portal system is generally confirmatory and can assess extension of thrombus into the mesenteric veins and exclude tumor thrombus in patients with cirrhosis. EUS may be helpful in some cases. In patients with jaundice, magnetic resonance cholangiography may demonstrate compression of the bile duct by a large portal cavernoma (portal biliopathy), a finding that may be more common in patients with an underlying hypercoagulable state than in those without one. In patients with pylephlebitis, CT may demonstrate an intra-abdominal source of infection, thrombosis or gas in the portal venous system, or a hepatic abscess.

D. Other Studies

Endoscopy shows esophageal or gastric varices. Needle biopsy of the liver may be indicated to diagnose schistosomiasis, nodular regenerative hyperplasia, and noncirrhotic portal fibrosis and may demonstrate sinusoidal dilatation. A low liver stiffness measurement by elastography may help distinguish noncirrhotic portal hypertension from cirrhosis.

Treatment

If splenic vein thrombosis is the cause of variceal bleeding, splenectomy is curative. For other causes of noncirrhotic portal hypertension, band ligation followed by beta-blockers to reduce portal pressure is initiated for variceal bleeding, with portosystemic shunting (including TIPS) reserved for failures of endoscopic therapy; rarely, progressive liver dysfunction requires liver transplantation. Anticoagulation, particularly with low-molecular-weight or unfractionated heparin, or thrombolytic therapy may be indicated for isolated acute portal vein thrombosis (and leads to at least partial recanalization in up to 75% of cases when started within 6 months of thrombosis) and possibly for acute splenic vein thrombosis; an oral anticoagulant is continued long-term if a hypercoagulable disorder is identified or if an acute portal vein thrombosis extends into the mesenteric veins. The decision to prescribe an anticoagulant for a patient with cirrhosis and portal vein thrombosis depends on the presence of ascites, the patient's fall risk, the extent and progression of the clot, and the patient's candidacy for liver transplantation. Partial portal vein thrombosis may resolve in 30–50% of cases. There is a paucity of data on the use of direct-acting oral anticoagulants in patients with cirrhosis and portal vein thrombosis. The use of enoxaparin to prevent portal vein thrombosis and hepatic decompensation in patients with cirrhosis has shown promise.

When to Refer

All patients with noncirrhotic portal hypertension should be referred.

Northup PG et al. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021;73:366. [PMID: 33219529]

Senzolo M et al. Current knowledge and management of portal vein thrombosis in cirrhosis. J Hepatol. 2021;75:442. [PMID: 33930474]

Simonetto DA et al. ACG Clinical Guideline: disorders of the hepatic and mesenteric circulation. Am J Gastroenterol. 2020;115:18. [PMID: 31895720]

PYOGENIC HEPATIC ABSCESS

ESSENTIALS OF DIAGNOSIS

- Fever, right upper quadrant pain, jaundice.
- Often occur in setting of biliary disease, but up to 40% are "cryptogenic" in origin.
- Detected by imaging studies.

General Considerations

The incidence of liver abscess is 3.6 per 100,000 population in the United States and has increased since the 1990s. The liver can be invaded by bacteria via (1) the

bile duct (acute "suppurative" [formerly ascending] cholangitis); (2) the portal vein (pylephlebitis); (3) the hepatic artery, secondary to bacteremia; (4) direct extension from an infectious process; and (5) traumatic implantation of bacteria through the abdominal wall or GI tract (eg, a fish or chicken bone). Risk factors for liver abscess include older age and male sex. Predisposing conditions and factors include presence of malignancy, diabetes mellitus, IBD, and cirrhosis; necessity for liver transplantation; endoscopic sphincterotomy; and use of a PPI. Statin use may reduce the risk of pyogenic liver abscess. Pyogenic liver abscess has been observed to be associated with a subsequent increased risk of GI malignancy and hepatocellular carcinoma.

Acute cholangitis resulting from biliary obstruction due to a stone, stricture, or neoplasm is the most common identifiable cause of hepatic abscess in the United States. In 10% of cases, liver abscess is secondary to appendicitis or diverticulitis. At least 40% of abscesses have no demonstrable cause and are classified as cryptogenic; a dental source is identified in some cases. The most frequently encountered organisms are *E coli, Klebsiella pneumoniae, Proteus vulgaris, Enterobacter aerogenes*, and multiple microaerophilic and anaerobic species (eg, *Streptococcus anginosus* [also known as *S milleri*]). Liver abscess caused by virulent strains of *K pneumoniae* may be associated with thrombophlebitis of the portal or hepatic veins and hematogenously spread septic ocular or CNS complications; the abscess may be gas-forming, associated with diabetes mellitus, and result in a high mortality rate. *Staphylococcus aureus* is usually the causative organism in patients with chronic granulomatous disease. Uncommon causative organisms include *Salmonella, Haemophilus, Yersinia*, and *Listeria*. Hepatic candidiasis, tuberculosis, and actinomycosis are seen in immunocompromised patients and those with hematologic malignancies. Rarely, hepatocellular carcinoma can present as a pyogenic abscess because of tumor necrosis, biliary obstruction, and superimposed bacterial infection (see Chapter 39); even more rarely, liver abscess may be the result of a necrotic liver metastasis. The possibility of an amoebic liver abscess must always be considered (see Chapter 35).

Clinical Findings

A. Symptoms and Signs

The presentation is often insidious. Fever (either steady or spiking fever) is almost always present and may antedate other symptoms or signs. Pain may be a prominent complaint and is localized to the right upper quadrant or epigastric area. Jaundice and tenderness in the right upper abdomen are the chief physical findings. The risk of AKI is increased.

B. Laboratory Findings

Laboratory examination reveals leukocytosis with a shift to the left. Liver biochemical tests are nonspecifically abnormal. Blood cultures are positive in 50–100% of cases.

C. Imaging

Chest films usually reveal elevation of the diaphragm if the abscess is in the right lobe of the liver. Ultrasonography, CT, or MRI may reveal the presence of intrahepatic lesions. On MRI, characteristic findings include high signal intensity on T2-weighted images and rim enhancement. The characteristic CT appearance of hepatic candidiasis, usually seen in the setting of systemic candidiasis, is that of multiple "bull's-eyes," but imaging studies may be negative in neutropenic patients.

Treatment

Treatment should consist of antimicrobial agents (generally a third-generation cephalosporin such as ceftriaxone 2 g intravenously every 24 hours and metronidazole 500 mg intravenously every 6 hours) that are effective against coliform organisms and anaerobes. Antibiotics are administered for 2–3 weeks, and sometimes for up to 6 weeks. If the abscess is at least 5 cm in diameter or the response to antibiotic therapy is not rapid, intermittent needle aspiration, percutaneous or EUS-guided catheter drainage or stent placement or, if necessary, surgical (eg, laparoscopic) drainage should be done. Other suggested indications for abscess drainage are patient age of at least 55 years, symptom duration of at least 7 days, and involvement of two lobes of the liver. The underlying source (eg, biliary disease, dental infection) should be identified and treated. The mortality rate is still substantial (at least 5% in most studies) and is highest in patients with underlying biliary malignancy or severe multiorgan dysfunction. Other risk factors for mortality include older age, cirrhosis, CKD, and other cancers. Hepatic candidiasis often responds to intravenous amphotericin B (total dose of 2–9 g). Fungal abscesses are associated with mortality rates of up to 50% and are treated with intravenous amphotericin B and drainage.

When to Admit

Nearly all patients with pyogenic hepatic abscess should be hospitalized.

Mukthinuthalapati VVPK et al. Risk factors, management, and outcomes of pyogenic liver abscess in a US safety net hospital. Dig Dis Sci. 2020;65:1529. [PMID: 31559551]

BENIGN LIVER NEOPLASMS

Benign neoplasms of the liver must be distinguished from hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and metastases (see Chapter 39). The most common benign neoplasm of the liver is the **cavernous hemangioma,** often an incidental finding on ultrasonography or CT. This lesion may enlarge in women who take hormonal therapy and must be differentiated from other space-occupying intrahepatic lesions, usually by contrast-enhanced MRI, CT, or ultrasonography. Rarely, fine-needle biopsy is necessary to differentiate these lesions and does

not appear to carry an increased risk of bleeding. Surgical resection of cavernous hemangiomas is infrequently necessary but may be required for abdominal pain or rapid enlargement, to exclude malignancy, or to treat Kasabach-Merritt syndrome (consumptive coagulopathy complicating a hemangioendothelioma or rapidly growing hemangioma, usually in infants).

In addition to rare instances of sinusoidal dilatation and peliosis hepatis, two distinct benign lesions with characteristic clinical, radiologic, and histopathologic features are focal nodular hyperplasia and hepatocellular adenoma. **Focal nodular hyperplasia** occurs at all ages and in both sexes and is probably not caused by oral contraceptives. It is often asymptomatic and appears as a hypervascular mass, often with a central hypodense "stellate" scar on contrast-enhanced ultrasonography, CT, or MRI. Focal nodular hyperplasia may also occur in patients with cirrhosis, with exposure to certain drugs such as azathioprine, and with antiphospholipid syndrome. The prevalence of hepatic hemangiomas is increased in patients with focal nodular hyperplasia.

Hepatocellular adenoma occurs most commonly in women in the third and fourth decades of life and is usually caused by oral contraceptives; acute abdominal pain may occur if the tumor undergoes necrosis or hemorrhage. The tumor may be associated with pathogenic variants in a variety of genes, some of which are associated with an increased risk of malignant transformation. Rare instances of multiple hepatocellular adenomas in association with maturity-onset diabetes of the young occur in families with a germline pathogenic variant in *HNF1alpha.* Hepatocellular adenomas also occur in patients with glycogen storage disease and familial adenomatous polyposis. The tumor is hypovascular.

Cystic neoplasms of the liver, such as cystadenoma and cystadenocarcinoma, must be distinguished from simple and echinococcal cysts, Von Meyenburg complexes (hamartomas), and polycystic liver disease.

Clinical Findings

The only physical finding in focal nodular hyperplasia or hepatocellular adenoma is a palpable abdominal mass in a minority of cases. Liver function is usually normal. Contrast-enhanced ultrasonography, arterial phase helical CT, and especially multiphase dynamic MRI with contrast can distinguish an adenoma from focal nodular hyperplasia without the need for biopsy in 80–90% of cases and may suggest a specific subtype of adenoma (eg, homogeneous fat pattern in *HNF1alpha*-variant adenomas and marked and persistent arterial enhancement in inflammatory adenomas).

Treatment

Oral contraceptives should not necessarily be discontinued in women who have focal nodular hyperplasia, although affected women who continue taking oral contraceptives should have annual ultrasonography for 2–3 years to ensure that the lesion is not enlarging. The prognosis is excellent.

Hepatocellular adenoma may undergo bleeding, necrosis, and rupture, often after hormone therapy; in the third trimester of pregnancy; or in men, in whom the rate of malignant transformation is high. A lesion less than 5 cm in diameter, however, poses little risk of complications to a pregnant woman, who should undergo ultrasonography during each trimester and 12 weeks postpartum. Resection is advised in all affected men and in women in whom the tumor causes symptoms or is 5 cm or greater in diameter, even in the absence of symptoms. If an adenoma is less than 5 cm in size, resection is also recommended if a beta-catenin gene pathogenic variant is present in a biopsy sample. In selected cases, laparoscopic resection or percutaneous radiofrequency ablation may be feasible. Rarely, liver transplantation is required. Regression of benign hepatic tumors may follow cessation of oral contraceptives. Transarterial embolization is the initial treatment for adenomas complicated by hemorrhage or rupture.

When to Refer

- Diagnostic uncertainty.
- For surgery.

When to Admit

- Severe pain.
- Rupture.

Herman P et al. Guidelines for the treatment of hepatocellular adenoma in the era of molecular biology: an experience-based surgeons' perspective. J Gastrointest Surg. 2021;25:1494. [PMID: 32666496]

Klompenhouwer AJ et al. New insights in the management of hepatocellular adenoma. Liver Int. 2020;40:1529. [PMID: 32464711]

Myers L et al. Focal nodular hyperplasia and hepatic adenoma: evaluation and management. Clin Liver Dis. 2020;24:389. [PMID: 32620279]

Yataco ML et al. Management of the incidental liver lesion. Am J Gastroenterol. 2021;116:855. [PMID: 33298700]

DISEASES OF THE BILIARY TRACT

See Chapter 39 for Carcinoma of the Biliary Tract.

CHOLELITHIASIS (Gallstones)

ESSENTIALS OF DIAGNOSIS

- Often asymptomatic.
- Classic biliary pain ("episodic gallbladder pain") characterized by infrequent episodes of steady severe pain in epigastrium or right upper quadrant with radiation to right scapula.
- Gallstones detected on ultrasonography.

General Considerations

Gallstones are more common in women than in men and increase in incidence in both sexes and all races with age. In the United States, the prevalence of gallstones is 8.6% in

women and 5.5% in men. The highest rates are in persons over age 60, and rates are higher in Mexican American persons than in White and Black persons who are not of Latinx descent. Although cholesterol gallstones are less common in Black persons, cholelithiasis attributable to hemolysis occurs in over a third of individuals with sickle cell disease. Persons who are native to either the northern or southern hemisphere have a high rate of cholesterol cholelithiasis. As many as 75% of Pima and other American Indian women over 25 years of age have cholelithiasis. Obesity is a risk factor for gallstones, especially in women. Rapid weight loss, as occurs after bariatric surgery, also increases the risk of symptomatic gallstone formation. Diabetes mellitus, glucose intolerance, and insulin resistance are risk factors for gallstones, and a high intake of carbohydrate and high dietary glycemic load increase the risk of cholecystectomy in women. Hypertriglyceridemia may promote gallstone formation by impairing gallbladder motility. The prevalence of gallbladder disease is increased in men (but not women) with cirrhosis and HCV infection. Moreover, cholecystectomy has been reported to be associated with an increased risk of NAFLD and cirrhosis, possibly because gallstones and liver disease share risk factors. Gallstone disease is associated with increased overall, cardiovascular, and cancer mortality.

The incidence of gallstones is high in individuals with Crohn disease; approximately one-third of those with inflammatory involvement of the terminal ileum have gallstones due to disruption of bile salt resorption that results in decreased solubility of the bile. Drugs such as clofibrate, octreotide, and ceftriaxone can cause gallstones. Prolonged fasting (over 5–10 days) can lead to formation of biliary "sludge" (microlithiasis), which usually resolves with refeeding but can lead to gallstones or biliary symptoms. Pregnancy, particularly in obese women and those with insulin resistance, is associated with an increased risk of gallstones and of symptomatic gallbladder disease. Hormone replacement therapy appears to increase the risk of gallbladder disease and need for cholecystectomy; the risk is lower with transdermal than oral therapy. Gallstones detected by population screening have been reported to be associated with an increased risk of right-sided colon cancers. A low-carbohydrate diet and a Mediterranean diet as well as physical activity and cardiorespiratory fitness may help prevent gallstones. Consumption of caffeinated coffee appears to protect against gallstones in women, and a high intake of magnesium and of polyunsaturated and monounsaturated fats reduces the risk of gallstones in men. A diet high in fiber and rich in fruits and vegetables and statin use reduce the risk of cholecystectomy, particularly in women. Aspirin and other NSAIDs may protect against gallstones.

Gallstones are classified according to their predominant chemical composition as cholesterol or calcium bilirubinate stones. The latter comprise less than 20% of the gallstones found in patients in the United States or Europe but 30–40% of gallstones found in patients in Japan.

Clinical Findings

Table 16–9 lists the clinical and laboratory features of several diseases of the biliary tract as well as their treatment. Cholelithiasis is frequently asymptomatic and is discovered during a routine imaging study, surgery, or autopsy. Symptoms (biliary [or "episodic gallbladder"] pain) develop in 10–25% of patients (1–4% annually), and acute cholecystitis develops in 20% of these symptomatic persons over time. Risk factors for the development of symptoms or complications include female sex; young age; awareness of having gallstones; and large, multiple, and older stones. Occasionally, small intestinal obstruction due to "gallstone ileus" (or Bouveret syndrome when the obstructing stone is in the pylorus or duodenum) presents as the initial manifestation of cholelithiasis.

Treatment

NSAIDs (eg, diclofenac 50–75 mg intramuscularly) can be used to relieve biliary pain. Laparoscopic cholecystectomy is the treatment of choice for symptomatic gallbladder disease. Pain relief after cholecystectomy is most likely in patients with episodic pain (generally once a month or less), pain lasting 30 minutes to 24 hours, pain in the evening or at night, and the onset of symptoms 1 year or less before presentation. Patients may go home within 1 day of the procedure and return to work within days (instead of weeks for those undergoing open cholecystectomy). The procedure is often performed on an outpatient basis and is suitable for most patients, including those with acute cholecystitis. Conversion to a conventional open cholecystectomy may be necessary in 2–8% of cases (higher for acute cholecystitis than for uncomplicated cholelithiasis). Bile duct injuries occur in 0.1% of cases done by experienced surgeons, and the overall complication rate is 11% and correlates with the patient's comorbidities, duration of surgery, and emergency admissions for gallbladder disease prior to cholecystectomy. There is generally no need for prophylactic cholecystectomy in an asymptomatic person unless the gallbladder is calcified, gallstones are 3 cm or greater in diameter, or the patient is a Native American or a candidate for bariatric surgery or cardiac transplantation. Cholecystectomy may increase the risk of esophageal, proximal small intestinal, and colonic adenocarcinomas as well as hepatocellular carcinoma because of increased duodenogastric reflux and changes in intestinal exposure to bile. In pregnant patients, a conservative approach to biliary pain is advised, but for patients with repeated attacks of biliary pain or acute cholecystitis, cholecystectomy can be performed—even by the laparoscopic route—preferably in the second trimester. Enterolithotomy alone is considered adequate treatment in most patients with gallstone ileus.

Ursodeoxycholic acid is a bile salt that when given orally for up to 2 years dissolves some cholesterol stones and may be considered in occasional, selected patients who refuse cholecystectomy. The dose is 8–10 mg/kg in two or three divided doses daily. It is most effective in patients with a functioning gallbladder, as determined by gallbladder visualization on oral cholecystography, and multiple small "floating" gallstones (representing not more than 15% of patients with gallstones). In half of patients, gallstones recur within 5 years after treatment is stopped.

Table 16–9. Diseases of the biliary tract.

	Clinical Features	Laboratory Features	Diagnosis	Treatment
Asymptomatic gallstones	Asymptomatic	Normal	Ultrasonography	None
Symptomatic gallstones	Biliary pain	Normal	Ultrasonography	Laparoscopic cholecystectomy
Cholesterolosis of gallbladder	Usually asymptomatic	Normal	Oral cholecystography	None
Adenomyomatosis	May cause biliary pain	Normal	Oral cholecystography	Laparoscopic cholecystectomy if symptomatic
Porcelain gallbladder	Usually asymptomatic, high risk of gallbladder cancer	Normal	Radiograph or CT	Laparoscopic cholecystectomy
Acute cholecystitis	Epigastric or right upper quadrant pain, nausea, vomiting, fever, Murphy sign	Leukocytosis	Ultrasonography, HIDA scan	Antibiotics, laparoscopic cholecystectomy
Chronic cholecystitis	Biliary pain, constant epigastric or right upper quadrant pain, nausea	Normal	Ultrasonography (stones), oral cholecystography (nonfunctioning gallbladder)	Laparoscopic cholecystectomy
Choledocholithiasis	Asymptomatic or biliary pain, jaundice, fever; gallstone pancreatitis	Cholestatic liver biochemical tests; leukocytosis and positive blood cultures in cholangitis; elevated amylase and lipase in pancreatitis	Ultrasonography (dilated ducts), EUS, MRCP, ERCP	Endoscopic sphincterotomy and stone extraction; antibiotics for cholangitis

ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; HIDA, hepatic iminodiacetic acid; MRCP, magnetic resonance cholangiopancreatography.

Ursodeoxycholic acid, 500–600 mg daily, and diets higher in fat reduce the risk of gallstone formation with rapid weight loss. Lithotripsy in combination with bile salt therapy for single radiolucent stones smaller than 20 mm in diameter was an option in the past but is no longer generally used in the United States.

When to Refer

Patients should be referred when they require surgery.

Gutt C et al. The treatment of gallstone disease. Dtsch Arztebl Int. 2020;117:148. [PMID: 32234195]
Sutherland JM et al. A cost-utility study of laparoscopic cholecystectomy for the treatment of symptomatic gallstones. J Gastrointest Surg. 2020;24:1314. [PMID: 31144191]

ACUTE CHOLECYSTITIS

ESSENTIALS OF DIAGNOSIS

- Steady, severe pain and tenderness in the right hypochondrium or epigastrium.
- Nausea and vomiting.
- Fever and leukocytosis.

General Considerations

Cholecystitis is associated with gallstones in over 90% of cases. It occurs when a stone becomes impacted in the cystic duct and inflammation develops behind the obstruction. Acalculous cholecystitis should be considered when unexplained fever or right upper quadrant pain occurs within 2–4 weeks of major surgery or in a critically ill patient who has had no oral intake for a prolonged period; multiorgan failure is often present. Acute cholecystitis may be caused by infectious agents (eg, cytomegalovirus, cryptosporidiosis, microsporidiosis) in patients with AIDS or by vasculitis (eg, polyarteritis nodosa, Henoch-Schönlein purpura).

Clinical Findings

A. Symptoms and Signs

The acute attack is often precipitated by a large or fatty meal and is characterized by the sudden appearance of steady pain localized to the epigastrium or right hypochondrium, which may gradually subside over a period of 12–18 hours. Vomiting occurs in about 75% of patients and in half of instances affords variable relief. Fever is typical. Right upper quadrant abdominal tenderness (often with a Murphy sign, or inhibition of inspiration by pain on palpation of the right upper quadrant) is almost always present

and is usually associated with muscle guarding and rebound tenderness (Table 16–9). A palpable gallbladder is present in about 15% of cases. Jaundice is present in about 25% of cases and, when persistent or severe, suggests the possibility of choledocholithiasis.

B. Laboratory Findings

The WBC count is usually high (12,000–15,000/mcL [12–15 × 10^9/L]). Total serum bilirubin values of 1–4 mg/dL (17.1–68.4 mcmol/L) may be seen even in the absence of bile duct obstruction. Serum aminotransferase and alkaline phosphatase levels are often elevated—the former as high as 300 U/mL, and even higher when associated with acute cholangitis. Serum amylase may also be moderately elevated.

C. Imaging

Plain films of the abdomen may show radiopaque gallstones in 15% of cases. Right upper quadrant abdominal ultrasonography, which is often performed first, may show gallstones but is not as sensitive for acute cholecystitis (sensitivity 67%, specificity 82%); findings suggestive of acute cholecystitis are gallbladder wall thickening, pericholecystic fluid, and a sonographic Murphy sign. ^{99m}Tc hepatobiliary imaging (using iminodiacetic acid compounds), also known as the hepatic iminodiacetic acid (HIDA) scan, is useful in demonstrating an obstructed cystic duct, which is the cause of acute cholecystitis in most patients. This test is reliable if the bilirubin is under 5 mg/dL (85.5 mcmol/L) (98% sensitivity and 81% specificity for acute cholecystitis). False-positive results can occur with prolonged fasting, liver disease, and chronic cholecystitis, and the specificity can be improved by intravenous administration of morphine, which induces spasm of the sphincter of Oddi. CT may show complications of acute cholecystitis, such as perforation or gangrene.

Differential Diagnosis

The disorders most likely to be confused with acute cholecystitis are perforated peptic ulcer, acute pancreatitis, appendicitis in a high-lying appendix, perforated colonic carcinoma or diverticulum of the hepatic flexure, liver abscess, hepatitis, pneumonia with pleurisy on the right side, and myocardial ischemia. Definite localization of pain and tenderness in the right upper quadrant, with radiation of pain around to the infrascapular area, strongly favors the diagnosis of acute cholecystitis. True cholecystitis without stones suggests acalculous cholecystitis.

Complications

A. Gangrene of the Gallbladder

Continuation or progression of right upper quadrant abdominal pain, tenderness, muscle guarding, fever, and leukocytosis after 24–48 hours suggests severe inflammation and possible gangrene of the gallbladder, resulting from ischemia due to splanchnic vasoconstriction and intravascular coagulation. Necrosis may occasionally develop without specific signs in persons who are obese, diabetic, older, or immunosuppressed. Gangrene may lead to gallbladder perforation, usually with formation of a pericholecystic abscess, and rarely to generalized peritonitis. Other serious acute complications include emphysematous cholecystitis (secondary infection with a gas-forming organism) and empyema.

B. Chronic Cholecystitis and Other Complications

Chronic cholecystitis results from repeated episodes of acute cholecystitis or chronic irritation of the gallbladder wall by stones and is characterized pathologically by varying degrees of chronic inflammation of the gallbladder. Calculi are usually present. In about 4–5% of cases, the villi of the gallbladder undergo polypoid enlargement due to deposition of cholesterol that may be visible to the naked eye ("strawberry gallbladder," cholesterolosis). In other instances, hyperplasia of all or part of the gallbladder wall may be so marked as to give the appearance of a myoma (adenomyomatosis). Hydrops of the gallbladder results when acute cholecystitis subsides but cystic duct obstruction persists, producing distention of the gallbladder with a clear mucoid fluid. Occasionally, a stone in the neck of the gallbladder may compress the common hepatic duct and cause jaundice (Mirizzi syndrome). Xanthogranulomatous cholecystitis is a rare, aggressive variant of chronic cholecystitis characterized by grayish-yellow nodules or streaks, representing lipid-laden macrophages, in the wall of the gallbladder and often presents with acute jaundice.

Cholelithiasis with chronic cholecystitis may be associated with acute exacerbations of gallbladder inflammation, bile duct stones, fistulization to the bowel, pancreatitis and, rarely, carcinoma of the gallbladder. Calcified (porcelain) gallbladder is associated with gallbladder carcinoma and is generally an indication for cholecystectomy; the risk of gallbladder cancer may be higher when calcification is mucosal rather than intramural.

Treatment

Acute cholecystitis usually subsides on a conservative regimen, including withholding oral feedings, intravenous fluids, analgesics, and intravenous antibiotics (generally a second- or third-generation cephalosporin such as ceftriaxone 1 g intravenously every 24 hours, with the addition of metronidazole, 500 mg intravenously every 6 hours), although the need for antibiotics has been questioned in patients undergoing immediate cholecystectomy. In severe cases, a fluoroquinolone such as ciprofloxacin, 400 mg intravenously every 12 hours, plus metronidazole, may be given. Morphine or meperidine may be administered for pain. Because of the high risk of recurrent attacks (up to 10% by 1 month and over 20% by 1 year), cholecystectomy—generally laparoscopically—should be performed within 24 hours of admission to the hospital for acute cholecystitis. Compared with delayed surgery, surgery within 24 hours is associated with a shorter length of stay, lower costs, and greater patient satisfaction. If nonsurgical treatment has been elected, the patient (especially if diabetic or older) must be watched carefully for recurrent symptoms, evidence of gangrene of the gallbladder, or cholangitis.

In high-risk patients, ultrasound-guided aspiration of the gallbladder, if feasible, percutaneous or EUS-guided cholecystostomy, or endoscopic insertion of a stent or nasobiliary drain into the gallbladder may postpone or even avoid the need for surgery. ERCP with transpapillary gallbladder drainage may be preferable in patients with coagulopathy or ascites. Immediate cholecystectomy is mandatory when there is evidence of gangrene or perforation. Surgical treatment of chronic cholecystitis is the same as for acute cholecystitis. If indicated, cholangiography can be performed during laparoscopic cholecystectomy. Choledocholithiasis can also be excluded by either preoperative or postoperative MRCP or ERCP.

Prognosis

The overall mortality rate of cholecystectomy is less than 0.2%, but hepatobiliary tract surgery is a more formidable procedure in older patients, in whom mortality rates are higher, as they are in persons with diabetes mellitus and cirrhosis. A technically successful surgical procedure in an appropriately selected patient is generally followed by complete resolution of symptoms.

When to Admit

All patients with acute cholecystitis should be hospitalized.

Podboy A et al. Comparison of EUS-guided endoscopic transpapillary and percutaneous gallbladder drainage for acute cholecystitis: a systematic review with network meta-analysis. Gastrointest Endosc. 2021;93:797. [PMID: 32987004]
Saumoy M et al. Endoscopic therapies for gallbladder drainage. Gastrointest Endosc. 2021;94:671. [PMID: 34344541]
Sobani ZA et al. Endoscopic transpapillary gallbladder drainage for acute cholecystitis. Dig Dis Sci. 2021;66:1425. [PMID: 32588249]
Sobani ZA et al. Endoscopic ultrasound-guided gallbladder drainage. Dig Dis Sci. 2021;66:2154. [PMID: 32749635]
Teoh AYB et al. EUS-guided gallbladder drainage versus laparoscopic cholecystectomy for acute cholecystitis: a propensity score analysis with 1-year follow-up data. Gastrointest Endosc. 2021;93:577. [PMID: 32615177]

PRE- & POSTCHOLECYSTECTOMY SYNDROMES

1. Precholecystectomy

In a small group of patients (mostly women) with biliary pain, conventional radiographic studies of the upper GI tract and gallbladder—including cholangiography—are unremarkable. Emptying of the gallbladder may be markedly reduced on gallbladder scintigraphy following injection of cholecystokinin; cholecystectomy may be curative in such cases. Histologic examination of the resected gallbladder may show chronic cholecystitis or microlithiasis. An additional diagnostic consideration is sphincter of Oddi dysfunction.

2. Postcholecystectomy

Following cholecystectomy, some patients complain of continuing symptoms, ie, right upper quadrant pain, flatulence, and fatty food intolerance. The persistence of symptoms in this group of patients suggests the possibility of an incorrect diagnosis prior to cholecystectomy, eg, esophagitis, pancreatitis, radiculopathy, or functional bowel disease. Choledocholithiasis or bile duct stricture should be ruled out. Pain may also be associated with dilatation of the cystic duct remnant, neuroma formation in the ductal wall, foreign body granuloma, anterior cutaneous nerve entrapment syndrome, or traction on the bile duct by a long cystic duct.

The clinical presentation of right upper quadrant pain, chills, fever, or jaundice suggests biliary tract disease. EUS is recommended to demonstrate or exclude a stone or stricture. Biliary pain associated with elevated liver biochemical tests or a dilated bile duct in the absence of an obstructing lesion suggests sphincter of Oddi dysfunction. Biliary manometry may be useful for documenting elevated baseline sphincter of Oddi pressures typical of sphincter dysfunction when biliary pain is associated with elevated liver biochemical tests (twofold) or a dilated bile duct (greater than 10 mm) ("sphincter disorder," formerly type II sphincter of Oddi dysfunction), but is not necessary when both are present ("sphincter stenosis," formerly type I sphincter of Oddi dysfunction) and is associated with a high risk of pancreatitis. In the absence of either elevated liver biochemical tests or a dilated bile duct ("functional pain," formerly type III sphincter of Oddi dysfunction), a nonbiliary source of symptoms should be suspected; biliary sphincterotomy does not benefit this group. (Analogous criteria have been developed for pancreatic sphincter dysfunction.) Biliary scintigraphy after intravenous administration of morphine and MRCP following intravenous administration of secretin have been studied as screening tests for sphincter dysfunction. Endoscopic sphincterotomy is most likely to relieve symptoms in patients with a sphincter disorder or stenosis, although many patients continue to have some pain. In some cases, treatment with a calcium channel blocker, long-acting nitrate, phosphodiesterase inhibitor (eg, vardenafil), duloxetine, or tricyclic antidepressant or possibly injection of the sphincter with botulinum toxin may be beneficial. The rate of psychosocial comorbidity with sphincter of Oddi dysfunction does not appear to differ from that of the general population. In refractory cases, surgical sphincteroplasty or removal of the cystic duct remnant may be considered.

When to Refer

Patients with sphincter of Oddi dysfunction should be referred for diagnostic procedures.

Miyatani H et al. Clinical course of biliary-type sphincter of Oddi dysfunction: endoscopic sphincterotomy and functional dyspepsia as affecting factors. Ther Adv Gastrointest Endosc. 2019;12:2631774519867184. [PMID: 31448369]
Smith ZL et al. The next EPISOD: trends in utilization of endoscopic sphincterotomy for sphincter of Oddi dysfunction from 2010–2019. Clin Gastroenterol Hepatol. 2022;20:e600. [PMID: 33161159]

CHOLEDOCHOLITHIASIS & CHOLANGITIS

ESSENTIALS OF DIAGNOSIS

- Often a history of biliary pain, which may be accompanied by jaundice.
- Occasional patients present with painless jaundice.
- Nausea and vomiting.
- Cholangitis should be suspected with fever followed by hypothermia and gram-negative shock, jaundice, and leukocytosis.
- Stones in bile duct most reliably detected by ERCP or EUS.

General Considerations

About 15% of patients with gallstones in the gallbladder have choledocholithiasis (bile duct stones). The percentage rises with age, and the frequency in older adults with gallstones may be as high as 50%. Bile duct stones usually originate in the gallbladder but may also form spontaneously in the bile duct after cholecystectomy. The risk is increased twofold in persons with a juxtapapillary duodenal diverticulum. Symptoms and possible cholangitis result if there is obstruction.

Clinical Findings

A. Symptoms and Signs

A history of biliary pain or jaundice may be obtained. Biliary pain results from rapid increases in bile duct pressure due to obstructed bile flow. The features that suggest the presence of a bile duct stone are (1) frequently recurring attacks of right upper abdominal pain that is severe and persists for hours, (2) chills and fever associated with severe pain, and (3) a history of jaundice associated with episodes of abdominal pain (Table 16–9). The combination of right upper quadrant pain, fever (and chills), and jaundice represents **Charcot triad** and denotes the classic picture of acute cholangitis. The addition of altered mental status and hypotension (**Reynolds pentad**) signifies acute suppurative cholangitis and is an endoscopic emergency. According to the Tokyo guidelines (revised in 2018), the diagnosis of acute cholangitis is established by an elevated WBC signifying systemic inflammation and elevated cholestatic liver biochemical test levels or imaging evidence of biliary dilatation, or both.

Hepatomegaly may be present in calculous biliary obstruction, and tenderness is usually present in the right upper quadrant and epigastrium. Bile duct obstruction lasting more than 30 days results in liver damage leading to cirrhosis. Hepatic failure with portal hypertension occurs in untreated cases. In a population-based study from Denmark, acute cholangitis was reported to be a marker of occult GI cancer.

B. Laboratory Findings

Acute obstruction of the bile duct typically produces a transient albeit striking increase in serum aminotransferase levels (often greater than 1000 U/L [20 mckat/L]). Bilirubinuria and elevation of the serum bilirubin are present if the bile duct remains obstructed; levels commonly fluctuate. Serum alkaline phosphatase levels rise more slowly. Not uncommonly, serum amylase elevations are present because of secondary pancreatitis. When extrahepatic obstruction persists for more than a few weeks, differentiation of obstruction from chronic cholestatic liver disease becomes more difficult. Leukocytosis is present in patients with acute cholangitis. Prolongation of the prothrombin time can result from the obstructed flow of bile to the intestine. In contrast to hepatocellular dysfunction, hypoprothrombinemia due to obstructive jaundice will respond to intravenous vitamin K, 10 mg, or water-soluble oral vitamin K (phytonadione), 5 mg, within 24–36 hours. In patients with acute calculous cholecystitis, predictors of concomitant choledocholithiasis are serum aminotransferase levels over three times the upper limit of normal, an alkaline phosphatase level above normal, a serum lipase over three times the upper limit of normal, a bilirubin of 1.8 mg/dL or more, and a bile duct diameter above 6 mm.

C. Imaging

Ultrasonography and CT may demonstrate dilated bile ducts, and radionuclide imaging may show impaired bile flow. EUS, helical CT, and magnetic resonance cholangiography are accurate in demonstrating bile duct stones and may be used in patients thought to be at intermediate risk for choledocholithiasis (age older than 55 years, cholecystitis, bile duct diameter greater than 6 mm on ultrasonography, serum bilirubin 1.8–4 mg/dL [30.78–68.4 mcmol/L], elevated serum liver enzymes, or pancreatitis). A decision analysis has suggested that magnetic resonance cholangiography is preferable when the risk of bile duct stones is low (less than 40%), and EUS is preferable when the risk is intermediate (40–91%). ERCP (occasionally with intraductal ultrasonography) or percutaneous transhepatic cholangiography provides the most direct and accurate means of determining the cause, location, and extent of obstruction, but in patients at intermediate risk of choledocholithiasis, initial cholecystectomy with intraoperative cholangiography results in a shorter length of hospital stay, fewer bile duct investigations, and no increase in morbidity. If the likelihood that obstruction is caused by a stone is high (bile duct stone seen on ultrasonography, serum bilirubin greater than 4 mg/dL [68.4 mcmol/L], or acute cholangitis), ERCP with sphincterotomy and stone extraction or stent placement is the procedure of choice; meticulous technique is required to avoid causing acute cholangitis. Because the sensitivity of these criteria for choledocholithiasis is only 80%, it is not unreasonable for magnetic resonance cholangiography or EUS to be done before ERCP.

Differential Diagnosis

The most common cause of obstructive jaundice is a bile duct stone. Next in frequency are neoplasms of the

pancreas, ampulla of Vater, or bile duct or an obstructed stent placed previously for decompression of an obstructing tumor. Extrinsic compression of the bile duct may result from metastatic carcinoma (usually from the GI tract or breast) involving porta hepatis lymph nodes or, rarely, from a large duodenal diverticulum. Gallbladder cancer extending into the bile duct often presents as obstructive jaundice. Chronic cholestatic liver diseases (PBC, sclerosing cholangitis, drug-induced) must be considered. Hepatocellular jaundice can usually be differentiated by the history, clinical findings, and liver biochemical tests, but liver biopsy is necessary on occasion. Recurrent pyogenic cholangitis should be considered in persons from Asia (and occasionally elsewhere) with intrahepatic biliary stones (particularly in the left ductal system) and recurrent cholangitis.

Treatment

In general, bile duct stones, even small ones, should be removed, even in an asymptomatic patient. A bile duct stone in a patient with cholelithiasis or cholecystitis is usually treated by endoscopic sphincterotomy and stone extraction followed by laparoscopic cholecystectomy within 72 hours in patients with cholecystitis and within 2 weeks in those without cholecystitis. In selected cases, laparoscopic cholecystectomy and ERCP can be performed in a single session. An alternative approach, which is also associated with a shorter duration of hospitalization in patients at intermediate risk for choledocholithiasis, is laparoscopic cholecystectomy and bile duct exploration.

For patients older than 70 years or poor-risk patients with cholelithiasis and choledocholithiasis, cholecystectomy may be deferred after endoscopic sphincterotomy because the risk of subsequent cholecystitis is low (although the risk of subsequent complications is lower when cholecystectomy is performed). ERCP with sphincterotomy, biliary drainage, and stone removal or stent placement generally within 48 hours, should be performed before cholecystectomy in patients with gallstones and cholangitis, jaundice (serum total bilirubin greater than 4 mg/dL [68.4 mcmol/L]), a dilated bile duct (greater than 6 mm), or stones in the bile duct seen on ultrasonography or CT. (Stones may ultimately recur in up to 12% of patients, particularly in older patients, when the bile duct diameter is 15 mm or greater or when brown pigment stones are found at the time of the initial sphincterotomy.) For bile duct stones 1 cm or more in diameter, endoscopic sphincterotomy followed by large balloon dilation has been recommended. Endoscopic balloon dilation of the sphincter of Oddi is otherwise considered in patients with coagulopathy because the risk of bleeding is lower with balloon dilation than with sphincterotomy. Balloon dilation is not associated with a higher rate of pancreatitis than endoscopic sphincterotomy if adequate dilation for more than 1 minute is carried out, and it may be associated with a lower rate of stone recurrence. An alternative approach is placement of a short fully covered metal stent to mitigate bleeding risk. EUS-guided biliary drainage and PTC with drainage are second-line approaches if ERCP fails or is not possible. In patients with biliary pancreatitis that resolves rapidly, the stone usually passes into the intestine, and ERCP prior to cholecystectomy is not necessary if intraoperative cholangiography is planned.

Choledocholithiasis discovered at laparoscopic cholecystectomy may be managed via laparoscopic or, if necessary, open bile duct exploration or by postoperative endoscopic sphincterotomy. Operative findings of choledocholithiasis are palpable stones in the bile duct, dilatation or thickening of the wall of the bile duct, or stones in the gallbladder small enough to pass through the cystic duct. Laparoscopic intraoperative cholangiography (or intraoperative ultrasonography) should be done at the time of cholecystectomy in patients with liver enzyme elevations but a bile duct diameter of less than 5 mm; if a ductal stone is found, the duct should be explored. In the postcholecystectomy patient with choledocholithiasis, endoscopic sphincterotomy with stone extraction is preferable to transabdominal surgery. Lithotripsy (endoscopic or external), peroral cholangioscopy (choledoscopy), or biliary stenting may be a therapeutic consideration for large stones. For the patient with a T tube and bile duct stone, the stone may be extracted via the T tube.

Postoperative antibiotics are not administered routinely after biliary tract surgery. Cultures of the bile are always taken at operation. If biliary tract infection was present preoperatively or is apparent at operation, ampicillin-sulbactam (3 g intravenously every 6 hours) or piperacillin-tazobactam (3.375 or 4.5 g intravenously every 6 hours) or a third-generation cephalosporin (eg, ceftriaxone, 1 g intravenously every 24 hours) is administered postoperatively and adjusted when the results of sensitivity tests on culture specimens are available. A T-tube cholangiogram should be done before the tube is removed, usually about 3 weeks after surgery.

Urgent ERCP with sphincterotomy and stone extraction (within 24–48 hours) is generally indicated for choledocholithiasis complicated by acute cholangitis and is preferred to surgery. Before ERCP, liver function should be evaluated thoroughly. The prothrombin time may be restored to normal by intravenous administration of vitamin K. For mild-to-moderately severe community-acquired acute cholangitis, ciprofloxacin (400 mg intravenously every 12 hours) penetrates well into bile and is effective treatment, with metronidazole (500 mg intravenously every 6–8 hours) for anaerobic coverage. An alternative regimen is ampicillin-sulbactam (3 g intravenously every 6 hours). Regimens for patients with severe or hospital-acquired acute cholangitis, and those potentially infected with an antibiotic-resistant pathogen, include intravenous piperacillin-tazobactam (3.375 or 4 g every 6 hours) or a carbapenem such as meropenem (1 g intravenously every 8 hours). Aminoglycosides (eg, gentamicin 5–7 mg/kg intravenously every 24 hours) may be added in cases of severe sepsis or septic shock but should not be given for more than a few days because the risk of aminoglycoside nephrotoxicity is increased in patients with cholestasis. Regimens that include drugs active against anaerobes are required when a biliary-enteric communication is present.

Emergent decompression of the bile duct, generally by ERCP, is required for patients who are septic or fail to improve on antibiotics within 12–24 hours. Medical therapy alone is most likely to fail in patients with tachycardia, a serum albumin less than 3 g/dL (30 g/L), marked hyperbilirubinemia, a high serum ALT level, a high WBC count, and a prothrombin time greater than 14 seconds on admission. If sphincterotomy cannot be performed, the bile duct can be decompressed by a biliary stent or nasobiliary catheter. Once decompression is achieved, antibiotics are generally continued for at least another 3 days. Cholecystectomy can be undertaken after resolution of cholangitis unless the patient remains unfit for surgery. Mortality from acute cholangitis has been reported to correlate with a high total bilirubin level, prolonged partial thromboplastin time, malnutrition, presence of a liver abscess, and unsuccessful ERCP.

When to Refer

All symptomatic patients with choledocholithiasis should be referred.

When to Admit

All patients with acute cholangitis should be hospitalized.

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BILIARY STRICTURE

Benign biliary strictures are the result of surgical (including liver transplantation) anastomosis or injury in about 95% of cases. The remainder of cases are caused by blunt external injury to the abdomen, pancreatitis, IgG_4-related disease, erosion of the duct by a gallstone, or prior endoscopic sphincterotomy.

Signs of injury to the duct may or may not be recognized in the immediate postoperative period. If complete occlusion has occurred, jaundice will develop rapidly; more often, however, a tear has been made accidentally in the duct, and the earliest manifestation of injury may be excessive or prolonged loss of bile from the surgical drains. Bile leakage resulting in a bile collection (biloma) may predispose to localized infection, which in turn accentuates scar formation and the ultimate development of a fibrous stricture.

Cholangitis is the most common complication of stricture. Typically, the patient experiences episodes of pain, fever, chills, and jaundice within a few weeks to months after cholecystectomy. Physical findings may include jaundice during an acute attack of cholangitis and right upper quadrant abdominal tenderness. Serum alkaline phosphatase is usually elevated. Hyperbilirubinemia is variable, fluctuating during exacerbations and usually remaining in the range of 5–10 mg/dL (85.5–171 mcmol/L). Blood cultures may be positive during an acute episode of cholangitis. Secondary biliary cirrhosis will inevitably develop if a stricture is not treated.

MRCP or multidetector CT is valuable in demonstrating the stricture and outlining the anatomy. ERCP is the first-line interventional approach and permits biopsy and cytologic specimens to exclude malignancy (in conjunction with EUS-guided fine-needle aspiration, an even more sensitive test for distal bile duct malignancy), sphincterotomy to allow a bile leak to close, and dilation (often repeated) and stent placement, thereby avoiding surgical repair in some cases. When ERCP is unsuccessful, dilation of a stricture may be accomplished by PTC or under EUS guidance. Placement of multiple plastic stents appears to be more effective than placement of a single stent. The use of fully covered self-expanding metal stents, which are more easily removed endoscopically than uncovered metal stents, as well as bioabsorbable stents, is an alternative to use of plastic stents and requires fewer ERCPs to achieve stricture resolution; stent migration may occur in 10% of cases. Uncovered metal stents, which often cannot be removed endoscopically, are generally avoided in benign strictures unless life expectancy is less than 2 years. Strictures related to chronic pancreatitis are more difficult than postsurgical strictures to treat endoscopically and may be best managed with a temporary covered metal stent. Following liver transplantation, endoscopic management is more successful for anastomotic than for nonanastomotic strictures. Results for nonanastomotic strictures may be improved with repeated dilations or the use of multiple plastic stents. Biliary strictures after live liver donor liver transplantation, particularly in patients with a late-onset (after 24 weeks) stricture or with intrahepatic biliary dilatation, are also challenging and require aggressive endoscopic therapy; in addition, the risk of post-ERCP pancreatitis appears to be increased.

When malignancy cannot be excluded with certainty, additional diagnostic approaches may be considered—if available—including intraductal ultrasonography, peroral cholangioscopy, confocal laser endomicroscopy, optical coherence tomography, fluorescence in situ hybridization, and, most recently, next-generation genetic sequencing. Differentiation from cholangiocarcinoma may ultimately require surgical exploration in 20% of cases. Operative treatment of a stricture frequently necessitates performance of an end-to-end ductal repair, choledochojejunostomy, or hepaticojejunostomy to reestablish bile flow into the intestine.

When to Refer

All patients with biliary stricture should be referred.

When to Admit

Patients with acute cholangitis should be hospitalized.

Han S et al. Combination of ERCP-based modalities increases diagnostic yield for biliary strictures. Dig Dis Sci. 2021;66:1276. [PMID: 32430658]
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PRIMARY SCLEROSING CHOLANGITIS

ESSENTIALS OF DIAGNOSIS

- Most common in men aged 20–50 years.
- Often associated with ulcerative colitis.
- Progressive jaundice, itching, and other features of cholestasis.
- Diagnosis based on characteristic cholangiographic findings.
- At least 10% risk of cholangiocarcinoma.

General Considerations

Primary sclerosing cholangitis is an uncommon disease thought to result from an increased immune response to intestinal endotoxins and characterized by diffuse inflammation of the biliary tract leading to fibrosis and strictures of the biliary system. From 60% to 70% of affected persons are male, usually 20–50 years of age (median age 41). The incidence is nearly 3.3 per 100,000 in Asian Americans, 2.8 per 100,000 in Latinx Americans, and 2.1 per 100,000 in Black persons, with an intermediate (and increasing) incidence in White persons and a prevalence of 16.2 per 100,000 population (21 per 100,000 men and 6 per 100,000 women) in the United States.

Primary sclerosing cholangitis is closely associated with IBD (more commonly ulcerative colitis than Crohn colitis), which is present in approximately two-thirds of patients with primary sclerosing cholangitis; however, clinically significant sclerosing cholangitis develops in only 1–4% of patients with ulcerative colitis. Smoking is associated with a decreased risk of primary sclerosing cholangitis in patients who also have IBD. Coffee consumption is also associated with a decreased risk of primary sclerosing cholangitis, and statin use is associated with improved outcomes in patients with primary sclerosing cholangitis. Women with primary sclerosing cholangitis may be more likely to have recurrent UTIs and less likely to use hormone replacement therapy than healthy controls. Associations with CVD and diabetes mellitus have been reported. Primary sclerosing cholangitis is associated with the histocompatibility antigens HLA-B8 and -DR3 or -DR4, and first-degree relatives of patients with primary sclerosing cholangitis have a fourfold increased risk of primary sclerosing cholangitis and a threefold increased risk of ulcerative colitis. A subset of patients with primary sclerosing cholangitis have increased serum IgG_4 levels and distinct HLA associations (with a poorer prognosis) but do not meet criteria for IgG_4-related sclerosing cholangitis. The diagnosis of primary sclerosing cholangitis may be difficult to make after biliary surgery.

Clinical Findings

A. Symptoms and Signs

Primary sclerosing cholangitis presents as progressive obstructive jaundice, frequently associated with fatigue, pruritus, anorexia, and indigestion. A patient's disease may be diagnosed in the presymptomatic phase because of an elevated alkaline phosphatase level or a subclinical phase based on abnormalities on magnetic resonance cholangiography despite normal liver enzyme levels. Complications of chronic cholestasis, such as osteoporosis, malabsorption of fat-soluble vitamins, and malnutrition, may occur late in the course. Risk factors for osteoporosis include older age, lower BMI, and longer duration of IBD. Esophageal varices on initial endoscopy are most likely in patients with a higher Mayo risk score based on age, bilirubin, albumin, and AST and a higher AST/ALT ratio, and new varices are likely to develop in those with a lower platelet count and higher bilirubin at 2 years. In patients with primary sclerosing cholangitis, ulcerative colitis is frequently characterized by rectal sparing and backwash ileitis.

B. Diagnostic Findings

The diagnosis of primary sclerosing cholangitis is generally made by MRCP, the sensitivity of which approaches that of ERCP. Characteristic cholangiographic findings are segmental fibrosis of bile ducts with saccular dilatations between strictures. Biliary obstruction by a stone or tumor should be excluded. Liver biopsy is not necessary for diagnosis when cholangiographic findings are characteristic. The disease may be confined to small intrahepatic bile ducts in about 15% of cases, in which case MRCP and ERCP are normal, and the diagnosis is suggested by liver biopsy findings. These patients have a longer survival than patients with involvement of the large ducts and do not appear to be at increased risk for cholangiocarcinoma unless large-duct sclerosing cholangitis develops (which occurs in about 20% over 7–10 years). Liver biopsy may show characteristic periductal fibrosis ("onion-skinning") and allows staging, which is based on the degree of fibrosis and which correlates with liver stiffness as measured by elastography. Perinuclear ANCA as well as antinuclear, anticardiolipin, antithyroperoxidase, and anti-*Saccharomyces cerevisiae* antibodies and rheumatoid factor are frequently detected in serum.

Occasional patients have clinical and histologic features of both sclerosing cholangitis and autoimmune hepatitis. Cholangitis in IgG_4-related disease is sometimes difficult to distinguish from primary sclerosing cholangitis (and even cholangiocarcinoma), is associated with autoimmune pancreatitis (see Chronic Pancreatitis), and is responsive to corticosteroids. A serum IgG_4 level more than four times

the upper limit of normal or an IgG_4:IgG_1 ratio of more than 0.24 strongly suggests IgG_4-related sclerosing cholangitis, but in up to one-third of cases, the serum IgG_4 level is normal. Primary sclerosing cholangitis must also be distinguished from idiopathic adulthood ductopenia (a rare disorder that affects young to middle-aged adults who manifest cholestasis resulting from loss of interlobular and septal bile ducts yet who have a normal cholangiogram. Primary sclerosing cholangitis must also be distinguished from other cholangiopathies (including PBC; cystic fibrosis; eosinophilic cholangitis; AIDS cholangiopathy; histiocytosis X; allograft rejection; graft-versus-host disease; ischemic cholangiopathy [often with biliary "casts," a rapid progression to cirrhosis, and a poor outcome] caused by hepatic artery thrombosis, shock, respiratory failure, or drugs, intra-arterial chemotherapy, sarcoidosis, and post-COVID cholangiopathy).

Complications

Cholangiocarcinoma may complicate the course of primary sclerosing cholangitis in up to 20% of cases (1.2% per year) and may be difficult to diagnose by cytologic examination or biopsy because of false-negative results. A serum CA 19-9 level above 100 U/mL is suggestive but not diagnostic of cholangiocarcinoma. Annual MRI with MRCP or right upper quadrant ultrasonography (MRCP is more sensitive than ultrasonography) and, by some guidelines but not others, serum CA 19-9 testing (a level of 20 is the threshold for further investigation) are recommended for surveillance, with ERCP and biliary cytology if the results are suggestive of malignancy. PET, peroral cholangioscopy, and confocal laser endomicroscopy may play roles in the early detection of cholangiocarcinoma. Patients with ulcerative colitis and primary sclerosing cholangitis are at high risk (tenfold higher than ulcerative colitis patients without primary sclerosing cholangitis) for colorectal neoplasia. The risks of gallstones, cholecystitis, gallbladder polyps, and gallbladder carcinoma appear to be increased in patients with primary sclerosing cholangitis.

Treatment

Episodes of acute bacterial cholangitis may be treated with ciprofloxacin (750 mg twice daily orally or intravenously). Ursodeoxycholic acid in standard doses (10–15 mg/kg/day orally) may improve liver biochemical test results but does not appear to alter the natural history. However, withdrawal of ursodeoxycholic acid may result in worsening of liver biochemical test levels and increased pruritus, and ursodeoxycholic acid in intermediate doses (17–23 mg/kg/day) has been reported to be beneficial.

Careful endoscopic evaluation of the biliary tract may permit balloon dilation of localized strictures, and repeated dilation of a dominant stricture may improve survival, although such patients have reduced survival compared with patients who do not have a dominant stricture. Short-term (2–3 weeks) placement of a stent in a major stricture also may relieve symptoms and improve biochemical abnormalities, with sustained improvement after the stent is removed, but may not be superior to balloon dilation alone; long-term stenting may increase the rate of complications such as cholangitis and is not recommended.

Cholecystectomy is indicated in patients with primary sclerosing cholangitis and a gallbladder polyp greater than 8 mm in diameter. In patients without cirrhosis, surgical resection of a dominant bile duct stricture may lead to longer survival than endoscopic therapy by decreasing the subsequent risk of cholangiocarcinoma. When feasible, extensive surgical resection of cholangiocarcinoma complicating primary sclerosing cholangitis may result in 5-year survival rates of greater than 50%. In patients with ulcerative colitis, primary sclerosing cholangitis is an independent risk factor for the development of colorectal dysplasia and cancer (especially in the right colon), and strict adherence to a colonoscopic surveillance program (yearly for those with ulcerative colitis and every 5 years for those without ulcerative colitis) is recommended. Whether treatment with ursodeoxycholic acid reduces the risk of colorectal dysplasia and carcinoma in patients with ulcerative colitis and primary sclerosing cholangitis is still uncertain. For patients with cirrhosis and clinical decompensation, liver transplantation is the treatment of choice; primary sclerosing cholangitis recurs in the graft in 30% of cases, with a possible reduction in the risk of recurrence when colectomy has been performed for ulcerative colitis before transplantation.

Prognosis

Survival of patients with primary sclerosing cholangitis averages 9–17 years, and up to 21 years in population-based studies. Adverse prognostic markers are older age, hepatosplenomegaly, higher serum bilirubin and AST levels, lower albumin levels, a history of variceal bleeding, a dominant bile duct stricture, and extrahepatic duct changes. Variceal bleeding is also a risk factor for cholangiocarcinoma. Patients in whom serum alkaline phosphatase levels decline by 40% or more (spontaneously, with ursodeoxycholic acid therapy, or after treatment of a dominant stricture) have longer transplant-free survival times than those in whom the alkaline phosphatase does not decline. Moreover, improvement in the serum alkaline phosphatase to less than 1.5 times the upper limit of normal is associated with a reduced risk of cholangiocarcinoma. Risk of progression can be predicted by three findings on MRI and MRCP: a cirrhotic appearance to the liver, portal hypertension, and enlarged perihepatic lymph nodes.

The Amsterdam-Oxford model has been proposed to predict transplant-free survival and is based on disease subtype (large- versus small-duct involvement), age at diagnosis, serum albumin, platelet count, serum AST, serum alkaline phosphatase, and serum bilirubin. Another promising scoring system is the UK-PSC risk score based on age, serum bilirubin, serum alkaline phosphatase, albumin, platelet count, presence of extrahepatic disease, and variceal hemorrhage. The PSC risk estimate tool (PREsTo) based on nine variables (bilirubin, albumin, alkaline phosphatase, platelets, AST, hemoglobin, sodium, patient age, and number of years since the diagnosis of primary sclerosing cholangitis) has been reported to accurately predict hepatic decompensation. Transplant-free survival can also

be predicted by serum levels of markers of liver fibrosis—hyaluronic acid, tissue inhibitor of metalloproteinase-1, and propeptide of type III procollagen. Reduced quality of life is associated with older age, large-duct disease, and systemic symptoms. Maternal primary sclerosing cholangitis is associated with preterm birth and cesarean section delivery; risk of congenital malformations is not increased. Interestingly, patients with milder ulcerative colitis tend to have more severe primary cholangitis and a higher rate of liver transplantation. Actuarial survival rates with liver transplantation are as high as 72% at 5 years, but rates are much lower once cholangiocarcinoma has developed. Following transplantation, patients have an increased risk of nonanastomotic biliary strictures and—in those with ulcerative colitis—colon cancer, and the disease recurs in 30%. The retransplantation rate is higher than that for PBC. Patients who are unable to undergo liver transplantation will ultimately require high-quality palliative care (see Chapter 5).

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DISEASES OF THE PANCREAS

See Chapter 39 for Carcinoma of the Pancreas and Periampullary Area.

ACUTE PANCREATITIS

ESSENTIALS OF DIAGNOSIS

- Abrupt onset of deep epigastric pain, often with radiation to the back.
- History of previous episodes, often related to alcohol intake.
- Nausea, vomiting, sweating, weakness.
- Abdominal tenderness and distention and fever.
- Leukocytosis, elevated serum amylase, elevated serum lipase.

General Considerations

The annual incidence of acute pancreatitis ranges from 110 to 140 per 100,000 population and has increased since 1990. Most cases of acute pancreatitis are related to biliary tract disease (45%) (a passed gallstone, usually 5 mm or less in diameter) or heavy alcohol intake (20%), with worldwide variations. The exact pathogenesis is not known but may include edema or obstruction of the ampulla of Vater, reflux of bile into pancreatic ducts, and direct injury of pancreatic acinar cells by prematurely activated pancreatic enzymes. Among the numerous other causes or associations are (1) hyperlipidemias (chylomicronemia, hypertriglyceridemia, or both); (2) hypercalcemia; (3) abdominal trauma (including surgery); (4) medications (including azathioprine, mercaptopurine, asparaginase, pentamidine, didanosine, valproic acid, tetracyclines, dapsone, isoniazid, metronidazole, estrogen and tamoxifen [by raising serum triglycerides], sulfonamides, mesalamine, celecoxib, sulindac, leflunomide, thiazides, simvastatin, fenofibrate, enalapril, methyldopa, procainamide, sitagliptin, exenatide, possibly corticosteroids, and others); (5) vasculitis; (6) infections (eg, hepatitis viruses, mumps, cytomegalovirus, *M avium intracellulare* complex, SARS-CoV-2); (7) peritoneal dialysis; (8) cardiopulmonary bypass, single- or double-balloon enteroscopy; (9) ERCP; and (10) a scorpion bite (rare). Medication-induced acute pancreatitis is generally dose-related and associated with worse outcomes than that due to other causes. In patients with pancreas divisum, a congenital anomaly in which the dorsal and ventral pancreatic ducts fail to fuse, acute pancreatitis may result from stenosis of the minor papilla with obstruction to flow from the accessory pancreatic duct, although concomitant gene variants, particularly in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, may account for acute pancreatitis in these patients. Acute pancreatitis may also result from an anomalous junction of the pancreaticobiliary duct (pancreaticobiliary malunion). Rarely, acute pancreatitis may be the presenting manifestation of a pancreatic or ampullary neoplasm or pancreatic cyst. Celiac disease appears to be associated with an increased risk of acute and chronic pancreatitis. Apparently "idiopathic" acute pancreatitis is often caused by occult biliary microlithiasis but unlikely to be caused by sphincter of Oddi dysfunction involving the pancreatic duct. Between 15% and 25% of cases are truly idiopathic. Smoking, high dietary glycemic load, and abdominal adiposity increase the risk of pancreatitis, and older age and obesity increase the risk of a severe course; vegetable consumption, dietary fiber, and use of statins may reduce the risk of pancreatitis, and coffee drinking may reduce the risk of nonbiliary pancreatitis.

Clinical Findings

A. Symptoms and Signs

Epigastric abdominal pain, generally abrupt in onset, is steady, boring, and severe and often made worse by walking and lying supine and better by sitting and leaning forward. The pain usually radiates into the back but may radiate to the right or left. Nausea and vomiting are usually present. Weakness, sweating, and anxiety are noted in severe attacks. There may be a history of alcohol intake or a heavy meal immediately preceding the attack or a history of milder similar episodes or biliary pain in the past.

The upper abdomen is tender, most often without guarding, rebound, or rigidity. The abdomen may be distended, and bowel sounds may be absent with associated ileus. Fever of 38.4–39°C, tachycardia, hypotension (even shock), pallor, and cool clammy skin are present in severe cases. Mild jaundice may be seen. Occasionally, an upper abdominal mass due to the inflamed pancreas or a pseudocyst may be palpated. AKI (usually prerenal azotemia) may occur early in the course of acute pancreatitis.

B. Laboratory Findings

Serum lipase and amylase are elevated—usually more than three times the upper limit of normal—within 24 hours in 90% of cases; their return to normal is variable depending on the severity of disease. Lipase remains elevated longer than amylase and is slightly more accurate for the diagnosis of acute pancreatitis. Leukocytosis (10,000–30,000/mcL [10–30 × 10^9/L]), proteinuria, granular casts, glycosuria (10–20% of cases), hyperglycemia, and elevated serum bilirubin may be present. BUN and serum alkaline phosphatase may be elevated and coagulation tests abnormal. An elevated serum creatinine level (greater than 1.8 mg/dL [149.94 mcmol/L]) at 48 hours is associated with the development of pancreatic necrosis. In patients with clear evidence of acute pancreatitis, a serum ALT level of more than 150 U/L (3 mkat/L) suggests biliary pancreatitis. A decrease in serum calcium may reflect saponification and correlates with severity of the disease. Levels lower than 7 mg/dL (1.75 mmol/L) (when serum albumin is normal) are associated with tetany and an unfavorable prognosis. Patients with acute pancreatitis caused by hypertriglyceridemia generally have fasting triglyceride levels above 1000 mg/dL (10 mmol/L) and often have other risk factors for pancreatitis; in some cases, the serum amylase is not elevated substantially because of an inhibitor in the serum of patients with marked hypertriglyceridemia that interferes with measurement of serum amylase. An early rise in the hematocrit value above 44% suggests hemoconcentration and predicts pancreatic necrosis. An elevated CRP concentration (greater than 150 mg/L [1500 mg/L]) at 48 hours suggests severe disease.

Other diagnostic tests that offer the possibility of simplicity, rapidity, ease of use, and low cost—including urinary trypsinogen-2, trypsinogen activation peptide, and carboxypeptidase B—are not widely available. In patients in whom ascites or a left pleural effusion develops, fluid amylase content is high. Electrocardiography may show ST–T wave changes.

C. Assessment of Severity

In addition to the individual laboratory parameters noted above, the severity of acute alcohol-associated pancreatitis can be assessed using several scoring systems (none of which has been shown to have high prognostic accuracy), including the **Ranson criteria** (Table 16–10). The **Sequential Organ Failure Assessment (SOFA)** score or **modified Marshall scoring system** can be used to assess injury to other organs, and the **Acute Physiology and Chronic Health Evaluation (APACHE II)** score is another tool for assessing severity. The severity of acute pancreatitis can also be predicted by the **Pancreatitis Activity Scoring System (PASS)** based on organ failure, intolerance to a solid diet, systemic inflammatory response syndrome, abdominal pain, and dose of intravenous morphine (or its equivalent) required to control pain. Another simple 5-point clinical scoring system (the **Bedside Index for Severity in Acute Pancreatitis,** or **BISAP**) based on **B**UN above 25 mg/dL (9 mmol/L), **I**mpaired mental status, **S**ystemic inflammatory response syndrome, **A**ge older than 60 years, and **P**leural effusion during the first 24 hours (before the onset of organ failure) identifies patients at increased risk for mortality. More simply, the presence of a systemic inflammatory response alone and an elevated BUN level on admission as well as a rise in BUN within the first 24 hours of hospitalization are independently associated with increased mortality; the greater the rise in BUN after admission, the greater the mortality rate. A model based on the change in serum amylase in the first 2 days after admission and the BMI has been proposed. The absence of rebound abdominal tenderness or guarding, a normal hematocrit value, and a normal serum creatinine level (the "**harmless acute pancreatitis score**," or **HAPS**) predict a nonsevere course with 98% accuracy. The **revised Atlanta classification** of the severity of acute pancreatitis uses the following three categories: (1) **mild** disease is the absence of organ failure and local ([peri] pancreatic necrosis or fluid collections) or systemic complications; (2) **moderate** disease is the presence of transient (under 48 hours) organ failure or local or systemic complications, or both; and (3) **severe** disease is the presence of persistent (48 hours or more) organ failure. A similar **"determinant-based" classification** also includes a

Table 16–10. Ranson criteria for assessing the severity of acute pancreatitis.

Three or more of the following predict a severe course complicated by pancreatic necrosis with a sensitivity of 60–80%

Age over 55 years
WBC count > 16 × 10^3/mcL (> 16 × 10^9/L)
Blood glucose > 200 mg/dL (> 11 mmol/L)
Serum LD > 350 U/L (> 7 mkat/L)
AST > 250 U/L (> 5 mkat/L)

Development of the following in the first 48 hours indicates a worsening prognosis

Hematocrit drop of more than 10 percentage points
BUN rise > 5 mg/dL (> 1.8 mmol/L)
Arterial Po_2 of < 60 mm Hg (< 7.8 kPa)
Serum calcium of < 8 mg/dL (< 0.2 mmol/L)
Base deficit over 4 mEq/L
Estimated fluid sequestration of > 6 L

Mortality rates correlate with the number of criteria present

Number of Criteria	Mortality Rate
0–2	1%
3–4	16%
5–6	40%
7–8	100%

category of **critical** acute pancreatitis characterized by both persistent organ failure and infected peripancreatic necrosis.

D. Imaging

Plain radiographs of the abdomen may show gallstones (if calcified), a "sentinel loop" (a segment of air-filled small intestine most commonly in the left upper quadrant), the "colon cutoff sign"—a gas-filled segment of transverse colon abruptly ending at the area of pancreatic inflammation—or focal linear atelectasis of the lower lobes of the lungs with or without pleural effusions. Ultrasonography is often not helpful in diagnosing acute pancreatitis because of intervening bowel gas but may identify gallstones in the gallbladder. Unenhanced CT is useful for demonstrating an enlarged pancreas when the diagnosis of pancreatitis is uncertain, differentiating pancreatitis from other possible intra-abdominal catastrophes, and providing an initial assessment of prognosis but is often unnecessary early in the course (Table 16–11). Rapid-bolus intravenous contrast-enhanced CT following aggressive volume resuscitation is of particular value after the first 3 days of severe acute pancreatitis for identifying areas of necrotizing pancreatitis and assessing the degree of necrosis (although the use of intravenous contrast may increase the risk of complications of pancreatitis and of AKI and should be avoided when the serum creatinine level is above 1.5 mg/dL [124.95 mcmol/L]). MRI appears to be a suitable alternative to CT. Perfusion CT on day 3 demonstrating areas of ischemia in the pancreas has been reported to predict the development of pancreatic necrosis. The presence of a fluid collection in the pancreas correlates with an increased mortality rate. CT-guided needle aspiration of areas of necrotizing pancreatitis after the third day may disclose infection, usually by enteric organisms, which typically requires debridement; however, the false-negative rate is 25%. The presence of gas bubbles on CT implies infection by gas-forming organisms. EUS is useful in identifying occult biliary disease (eg, small stones, sludge, microlithiasis), which is present in many patients with apparently idiopathic acute pancreatitis and is indicated in persons over age 40 to exclude malignancy. ERCP is generally not indicated after a first attack of acute pancreatitis unless there is associated cholangitis or jaundice or a bile duct stone is known to be present, but EUS or MRCP should be considered, especially after repeated attacks of idiopathic acute pancreatitis. Following a single attack of idiopathic acute pancreatitis, a negative EUS examination predicts a low risk of relapse.

Differential Diagnosis

Acute pancreatitis must be differentiated from an acutely perforated duodenal ulcer, acute cholecystitis, acute intestinal obstruction, leaking aortic aneurysm, renal colic, and acute mesenteric ischemia. Serum amylase may also be elevated in proximal intestinal obstruction, gastroenteritis, mumps not involving the pancreas (salivary amylase), and ectopic pregnancy and after administration of opioids and abdominal surgery. Serum lipase may also be elevated in many of these conditions.

Complications

Intravascular volume depletion secondary to leakage of fluids into the pancreatic bed and to ileus with fluid-filled loops of bowel may result in prerenal azotemia and even ATN without overt shock. This sequence usually occurs within 24 hours of the onset of acute pancreatitis and lasts 8–9 days. Some patients require renal replacement therapy.

According to the revised Atlanta classification, fluid collections and necrosis may be acute (within the first 4 weeks) or chronic (after 4 weeks) and sterile or infected. Chronic collections, including pseudocysts and walled-off necrosis, are characterized by encapsulation. Sterile or infected necrotizing pancreatitis may complicate the course in 5–10% of cases and accounts for most of the deaths. The risk of infection does not correlate with the extent of necrosis. Pancreatic necrosis is often associated with fever, leukocytosis, and, in some cases, shock and is associated with organ failure (eg, GI bleeding, respiratory failure, AKI) in 50% of cases. It may lead to complete transection of the pancreatic duct (disconnected pancreatic duct syndrome), which may result in recurrent fluid collections or persistent fistulae months or years after necrosis has resolved. Because infected pancreatic necrosis is often an indication for

Table 16–11. Estimated mortality rates of pancreatitis based on severity.

Point Value for Appearance of Pancreas Based on CT scan		Additional Points for Percentage of Pancreatic Necrosis		Estimated Mortality Rate Based on Total Points Sum	
Condition of Pancreas	Points	Percentage of Necrosis	Points	Total Points	Estimated Mortality Rate
Normal pancreas	0	0%	0	0	0%
Enlargement of pancreas	1 point	0%	0	1	0%
Inflammation of the pancreas or peripancreatic fat or both	2 points	< 30%	2 points	4	< 3%
Single new peripancreatic fluid collection	3 points	30–50%	4 points	7	> 6%
Two or more new peripancreatic fluid collections or retroperitoneal air	4 points	> 50%	6 points	10	~17%

debridement, fine-needle aspiration of necrotic tissue under CT guidance should be performed (if necessary, repeatedly) for Gram stain and culture.

A serious complication of acute pancreatitis is acute respiratory distress syndrome (ARDS); cardiac dysfunction may be superimposed. It usually occurs 3–7 days after the onset of pancreatitis in patients who have required large volumes of fluid and colloid to maintain blood pressure and urinary output. Most patients with ARDS require intubation, mechanical ventilation, and supplemental oxygen.

Pancreatic abscess (also referred to as infected or suppurative pseudocyst) is a suppurative process characterized by rising fever, leukocytosis, and localized tenderness and an epigastric mass usually 6 or more weeks into the course of acute pancreatitis. The abscess may be associated with a left-sided pleural effusion or an enlarging spleen secondary to splenic vein thrombosis. In contrast to infected necrosis, the mortality rate is low following drainage.

Pseudocysts, encapsulated fluid collections with high amylase content, commonly appear in pancreatitis when CT is used to monitor the evolution of an acute attack. Pseudocysts that are smaller than 6 cm in diameter often resolve spontaneously. They most commonly are within or adjacent to the pancreas but can present almost anywhere (eg, mediastinal, retrorectal) by extension along anatomic planes. Multiple pseudocysts are seen in 14% of cases. Pseudocysts may become secondarily infected, necessitating drainage as for an abscess. Pancreatic ascites may present after recovery from acute pancreatitis as a gradual increase in abdominal girth and persistent elevation of the serum amylase level in the absence of frank abdominal pain. Marked elevations in ascitic protein (greater than 3 g/dL) and amylase (greater than 1000 U/L [20 mkat/L]) concentrations are typical. The condition results from disruption of the pancreatic duct or drainage of a pseudocyst into the peritoneal cavity.

Rare complications of acute pancreatitis include hemorrhage caused by erosion of a blood vessel to form a pseudoaneurysm and by colonic necrosis. Portosplenomesenteric venous thrombosis frequently develops in patients with necrotizing acute pancreatitis but rarely leads to complications. Other local complications include abdominal compartment syndrome, intestinal ischemia, and gastric outlet obstruction. Chronic pancreatitis develops in about 10% of cases of acute pancreatitis. Diabetes mellitus and exocrine pancreatic insufficiency may develop after acute pancreatitis.

Treatment

A. Treatment of Acute Disease

1. Mild disease—In most patients, acute pancreatitis is a mild disease ("nonsevere acute pancreatitis") that subsides spontaneously within several days. The pancreas is "rested" by a regimen of withholding food and liquids by mouth, bed rest, and, in patients with moderately severe pain or ileus and abdominal distention or vomiting, nasogastric suction. Goal-directed therapy with early aggressive fluid resuscitation (one-third of the total 72-hour fluid volume administered within 24 hours of presentation, 250–500 mL/hour initially) may reduce the frequency of systemic inflammatory response syndrome and organ failure in this group of patients and appears to have the greatest benefit in patients with acute pancreatitis predicted to be mild in severity when started within 4 hours of the patient's arrival at the hospital. Lactated Ringer solution may be preferable to normal saline; however, overly aggressive fluid resuscitation may lead to morbidity as well.

Pain is controlled with meperidine, up to 100–150 mg intramuscularly every 3–4 hours as necessary. In those with severe liver or kidney dysfunction, the dose may need to be reduced. Morphine had been thought to cause sphincter of Oddi spasm but is now considered an acceptable alternative and, given the potential side effects of meperidine, may even be preferable. Oral intake of fluid and foods can be resumed when the patient is largely free of pain and has bowel sounds (even if the serum amylase is still elevated). Clear liquids are given first (this step may be skipped in patients with mild acute pancreatitis), followed by gradual advancement to a low-fat diet, guided by the patient's tolerance and by the absence of pain. Pain may recur on refeeding in 20% of patients.

Following recovery from acute biliary pancreatitis, laparoscopic cholecystectomy is generally performed, preferably during the same hospital admission, and is associated with a reduced rate of recurrent gallstone-related complications compared with delayed cholecystectomy. In selected cases endoscopic sphincterotomy alone may be done. In patients with recurrent pancreatitis associated with pancreas divisum, insertion of a stent in the minor papilla (or minor papilla sphincterotomy) may reduce the frequency of subsequent attacks, although complications of such therapy are frequent. In patients with recurrent acute pancreatitis attributed to pancreatic sphincter of Oddi dysfunction, biliary sphincterotomy alone is as effective as combined biliary and pancreatic sphincterotomy in reducing the frequency of recurrent acute pancreatitis, but chronic pancreatitis may still develop in treated patients. Hypertriglyceridemia with acute pancreatitis has been treated with combinations of insulin, heparin, apheresis, and hemofiltration, but the benefit of these approaches has not been proven.

2. Severe disease—In more severe pancreatitis—particularly necrotizing pancreatitis—there may be considerable leakage of fluids, necessitating large amounts of intravenous fluids (eg, 500–1000 mL/hour for several hours, then 250–300 mL/hour) to maintain intravascular volume. Risk factors for high levels of fluid sequestration include younger age, alcohol etiology, higher hematocrit value, higher serum glucose, and systemic inflammatory response syndrome in the first 48 hours of hospital admission. Hemodynamic monitoring in an ICU is required, and the importance of aggressive goal-directed intravenous hydration targeted to result in adequate urinary output, stabilization of blood pressure and heart rate, restoration of central venous pressure, and a modest decrease in hematocrit value cannot be overemphasized. Calcium gluconate must be given intravenously if there is evidence of hypocalcemia with tetany. Infusions of fresh frozen plasma or serum albumin may be necessary in patients with coagulopathy or

hypoalbuminemia. With colloid solutions, the risk of ARDS may be increased. If shock persists after adequate volume replacement (including packed red cells), vasopressors may be required. For the patient requiring a large volume of parenteral fluids, central venous pressure and blood gases should be monitored at regular intervals.

Enteral nutrition via a nasojejunal or possibly nasogastric feeding tube is preferable to parenteral nutrition in patients who will otherwise be without oral nutrition for at least 7–10 days and it reduces the risk of multiorgan failure and mortality when started within 48 hours of admission. However, it is not tolerated in some patients (eg, those with an ileus) and may not reduce the rates of infection and death compared with resumption of oral feeding after 72 hours. Parenteral nutrition (including lipids) should be considered in patients who have severe pancreatitis and ileus; glutamine supplementation appears to reduce the risk of infectious complications and mortality.

The routine use of antibiotics to prevent conversion of sterile necrotizing pancreatitis to infected necrosis is of no benefit and generally is not indicated in patients with less than 30% pancreatic necrosis. Imipenem (500 mg intravenously every 6 hours) or possibly cefuroxime (1.5 g intravenously three times daily, then 250 mg orally twice daily) administered for no more than 14 days to patients with sterile necrotizing pancreatitis has been reported in some studies to reduce the risk of pancreatic infection and mortality, but in general, prophylactic antibiotics are not recommended; meropenem and the combination of ciprofloxacin and metronidazole do not appear to reduce the frequency of infected necrosis, multiorgan failure, or mortality. When infected necrotizing pancreatitis is confirmed, imipenem or meropenem should be continued. Drug-resistant organisms are increasingly prevalent. In occasional cases, a fungal infection is found, and appropriate antifungal therapy should be prescribed.

NSAIDs (eg, indomethacin administered rectally) and aggressive hydration with lactated Ringer solution have been reported to reduce the frequency and severity of post-ERCP pancreatitis in persons at high risk, and rectal indomethacin is widely used, but studies of the benefit of indomethacin in unselected patients have yielded conflicting results. Placement of a stent across the pancreatic duct or orifice has been shown to reduce the risk of post-ERCP pancreatitis by 60–80% and is a common practice.

B. Treatment of Complications and Follow-Up

A surgeon should be consulted in all cases of severe acute pancreatitis. If the diagnosis is in doubt and investigation indicates a strong possibility of a serious surgically correctable lesion (eg, perforated peptic ulcer), exploratory laparotomy is indicated. When acute pancreatitis is found unexpectedly, it is usually wise to close without intervention. If the pancreatitis appears mild and cholelithiasis or microlithiasis is present, cholecystectomy or cholecystostomy may be justified. When severe pancreatitis results from choledocholithiasis and jaundice (serum total bilirubin above 5 mg/dL [85.5 mcmol/L]) or cholangitis is present, ERCP with endoscopic sphincterotomy and stone extraction is indicated. MRCP may be useful in selecting patients for therapeutic ERCP. Endoscopic sphincterotomy does not appear to improve the outcome of severe pancreatitis in the absence of cholangitis or jaundice.

Necrosectomy may improve survival in patients with necrotizing pancreatitis and clinical deterioration with multiorgan failure or lack of resolution by 4 weeks and is often indicated for infected necrosis, although a select group of relatively stable patients with infected pancreatic necrosis may be managed with antibiotics alone. The goal is to debride necrotic pancreas and surrounding tissue and establish adequate drainage. Outcomes are best if necrosectomy is delayed until the necrosis has organized, usually about 4 weeks after disease onset. A "step-up" approach in which nonsurgical endoscopic transluminal (transgastric or transduodenal) or percutaneous catheter drainage of walled-off pancreatic necrosis under radiologic guidance, with subsequent endoscopic and, if necessary, open surgical necrosectomy has been shown to reduce mortality and resource utilization in selected patients with necrotizing pancreatitis and confirmed or suspected secondary infection. In some cases, laparoscopic guidance (video-assisted retroperitoneal debridement) is an additional option, depending on local expertise. Lumen-apposing metal stents (LAMS) or double-pigtail plastic stents are used for endoscopic transluminal drainage, with removal of LAMS after 4 weeks to minimize the risk of complications. Treatment is labor intensive, and multiple procedures are often required, although costs and complication rates are lower than those for surgery. Endoscopic or surgical interventions may be required for chronic disconnected pancreatic duct syndrome.

The development of a pancreatic abscess is an indication for prompt percutaneous or surgical drainage. Chronic pseudocysts require endoscopic, percutaneous catheter, or surgical drainage when infected or associated with persisting pain, pancreatitis, or bile duct obstruction. For pancreatic infections, imipenem, 500 mg every 8 hours intravenously, is a good choice of antibiotic because it achieves bactericidal levels in pancreatic tissue for most causative organisms. Pancreatic duct leaks and fistulas may require endoscopic or surgical therapy.

Prognosis

Mortality rates for acute pancreatitis have declined from at least 10% to around 5% since the 1980s, but the mortality rate for severe acute pancreatitis (more than three Ranson criteria; see Table 16–10) remains at least 20%, with rates of 10% and 25% in those with sterile and infected necrosis, respectively. Severe acute pancreatitis is predicted by features of the systemic inflammatory response on admission; a persistent systemic inflammatory response is associated with a mortality rate of 25% and a transient response with a mortality rate of 8%. Half of the deaths, usually from multiorgan failure, occur within the first 2 weeks. Multiorgan failure is associated with a mortality rate of at least 30%, and if it persists beyond the first 48 hours, a mortality rate of over 50%. Later deaths occur because of complications of infected necrosis. The risk of death doubles when both organ failure and infected necrosis are present. Moreover, hospital-acquired infections increase the mortality of

acute pancreatitis, independent of severity. Readmission to the hospital for acute pancreatitis within 30 days may be predicted by a scoring system based on five factors during the index admission: eating less than a solid diet at discharge; nausea, vomiting, or diarrhea at discharge; pancreatic necrosis; use of antibiotics at discharge; and pain at discharge. Male sex, an alcohol etiology, and severe acute disease are risk factors. Recurrences are common (24%) in alcohol-associated pancreatitis, particularly in patients who smoke (40%), but can be reduced by repeated, regularly scheduled interventions to eliminate alcohol consumption and smoking after discharge from the hospital. A severe initial attack also increases the risk of recurrence and of subsequent exocrine pancreatic insufficiency. The risk of chronic pancreatitis following an episode of acute alcohol-associated pancreatitis is 8% in 5 years, 13% in 10 years, and 16% in 20 years, and the risk of diabetes mellitus is increased more than twofold over 5 years. Overall, chronic pancreatitis develops in 36% of patients with recurrent acute pancreatitis; alcohol use and smoking are principal risk factors. An association between a diagnosis of acute pancreatitis and long-term risk of pancreatic cancer has been reported.

When to Admit

Nearly all patients with acute pancreatitis should be hospitalized.

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CHRONIC PANCREATITIS

ESSENTIALS OF DIAGNOSIS

- Chronic or intermittent epigastric pain, steatorrhea, weight loss, abnormal pancreatic imaging.
- A mnemonic for the predisposing factors of chronic pancreatitis is TIGAR-O: toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, or obstructive.

General Considerations

The prevalence of chronic pancreatitis in the United States is 25–99 per 100,000 population with a peak in persons aged 46–55 years. Chronic pancreatitis occurs most often in patients with alcoholism (45–80% of all cases). The risk of chronic pancreatitis increases with the duration and amount of alcohol consumed, but pancreatitis develops in only 5–10% of heavy drinkers. Tobacco smoking is a risk factor for idiopathic chronic pancreatitis and has been reported to accelerate progression of alcohol-associated chronic pancreatitis. About 2% of patients with hyperparathyroidism develop pancreatitis. In tropical Africa and Asia, tropical pancreatitis, related in part to malnutrition, is the most common cause of chronic pancreatitis. By contrast, in Western societies, obesity can lead to pancreatic steatosis, which may lead ultimately to pancreatic exocrine and endocrine insufficiency and an increased risk of pancreatic cancer. A stricture, stone, or tumor obstructing the pancreas can lead to obstructive chronic pancreatitis. Autoimmune pancreatitis is associated with hypergammaglobulinemia (IgG_4 in particular), often with autoantibodies and other autoimmune diseases, and is responsive to corticosteroids. Affected persons are at increased risk for various cancers. Type 1 autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis, or simply autoimmune pancreatitis) is a multisystem disease, typically in a patient over age 60, characterized by lymphoplasmacytic infiltration and fibrosis on biopsy, associated bile duct strictures, retroperitoneal fibrosis, renal and salivary gland lesions, and a high rate of relapse after treatment. It is the pancreatic manifestation of IgG_4-related disease. Type 2 ("idiopathic duct-centric chronic pancreatitis") affects the pancreas alone, typically in a patient aged 40–50 years, and is characterized by intense duct-centric lymphoplasmacytic infiltration on biopsy, lack of systemic IgG_4 involvement, an association with IBD in 25% of cases, often a tumor-like mass, and a low rate of relapse after treatment. Between 10% and 30% of cases of chronic pancreatitis are idiopathic, with either early onset (median age 20) or late onset (median age 58). Genetic factors may predispose to chronic pancreatitis in nearly half of the early-onset cases and a quarter of the late-onset cases and include pathogenic variants of the *CFTR* gene, the pancreatic secretory trypsin inhibitory gene (*PSTI*, also known as the serine protease inhibitor, *SPINK1*), the chymotrypsin-C (*CTRC*) gene, and the genes for carboxypeptidase A1 (*CPA1*) and possibly uridine 5′-diphosphate glucuronosyltransferase (*UGT1A7*). A variant of the cationic trypsinogen gene on chromosome 7 (serine protease 1, *PRSS1*) is associated with hereditary pancreatitis, transmitted as an autosomal dominant trait with variable penetrance. A useful mnemonic for the predisposing factors to chronic pancreatitis is **TIGAR-O: T**oxic-metabolic, **I**diopathic, **G**enetic, **A**utoimmune, **R**ecurrent and severe acute pancreatitis, or **O**bstructive.

The pathogenesis of chronic pancreatitis may be explained by the SAPE (**S**entinel **A**cute **P**ancreatitis **E**vent) hypothesis by which the first (sentinel) acute pancreatitis event initiates an inflammatory process that results in injury and later fibrosis ("necrosis-fibrosis"). In many cases, chronic pancreatitis is a self-perpetuating disease characterized by chronic pain or recurrent episodes of acute pancreatitis and ultimately by pancreatic exocrine or endocrine insufficiency (sooner in alcohol-associated pancreatitis than in other types). After many years, chronic pain may resolve spontaneously or following surgery tailored to the cause of pain. Over 80% of adults develop diabetes mellitus within 25 years after the clinical onset of chronic pancreatitis.

Clinical Findings

A. Symptoms and Signs

Persistent or recurrent episodes of epigastric and left upper quadrant pain are typical. Anorexia, nausea, vomiting, constipation, flatulence, and weight loss are common. During attacks, tenderness over the pancreas, mild muscle guarding, and ileus may be noted. Attacks may last for only a few hours or for as long as 2 weeks; pain may eventually be almost continuous. Steatorrhea (as indicated by bulky, foul, fatty stools) may occur late in the course.

B. Laboratory Findings

Serum amylase and lipase may be elevated during acute attacks; however, normal values do not exclude the diagnosis. Serum alkaline phosphatase and bilirubin may be elevated owing to compression of the bile duct. Glycosuria may be present. Excess fecal fat may be demonstrated on chemical analysis of the stool. Exocrine pancreatic insufficiency generally is confirmed by response to therapy with pancreatic enzyme supplements; the secretin stimulation test can be used if available (and has a high negative predictive value for ruling out early acute chronic pancreatitis), as can detection of decreased fecal chymotrypsin or elastase levels, although the latter tests lack sensitivity and specificity. Vitamin B_{12} malabsorption is detectable in about 40% of patients, but clinical deficiency of vitamin B_{12} and fat-soluble vitamins is rare. Accurate diagnostic tests are available for the major trypsinogen gene pathogenic variants, but because of uncertainty about the mechanisms linking heterozygous *CFTR* and *PSTI* variants with pancreatitis, genetic testing for mutations in these two genes is recommended primarily in younger patients in whom the etiology of chronic pancreatitis is unclear. Elevated IgG_4 levels, ANA, antibodies to lactoferrin and carbonic anhydrase II, and other autoantibodies are often found in patients with autoimmune pancreatitis (especially type 1). Pancreatic biopsy, if necessary, shows a lymphoplasmacytic inflammatory infiltrate with characteristic IgG_4 immunostaining, which is also found in biopsy specimens of the major papilla, bile duct, and salivary glands, in type 1 autoimmune pancreatitis.

C. Imaging

CT or MRI is recommended as initial testing for diagnosis of chronic pancreatitis, although plain films show calcifications due to pancreaticolithiasis in 30% of affected patients. CT may show calcifications not seen on plain films as well as ductal dilatation and heterogeneity or atrophy of the gland. Occasionally, the findings raise suspicion of pancreatic cancer ("tumefactive chronic pancreatitis"). Secretin-enhanced MRCP may be considered in selected cases. When CT or MRI is inconclusive, EUS (with pancreatic tissue sampling) may be needed. Endoscopic ultrasonographic ("Rosemont") criteria for the diagnosis of chronic pancreatitis include hyperechoic foci with shadowing indicative of calculi in the main pancreatic duct and lobularity with honeycombing of the pancreatic parenchyma. ERCP is the most sensitive imaging study for chronic pancreatitis and may show dilated ducts, intraductal stones, strictures, or pseudocyst but is infrequently used for diagnosis alone; moreover, the results may be normal in patients with so-called minimal change pancreatitis. Histology is the gold standard for diagnosis when clinical suspicion is strong but imaging studies are inconclusive.

Characteristic imaging features of autoimmune pancreatitis include diffuse enlargement of the pancreas, a peripheral rim of hypoattenuation, and irregular narrowing of the main pancreatic duct. In the United States, the diagnosis of autoimmune pancreatitis is based on the **HISORt** criteria: **H**istology, **I**maging, **S**erology, other **O**rgan involvement, and **R**esponse to corticosteroid **T**herapy.

Complications

Opioid addiction is common. Other frequent complications include often brittle diabetes mellitus, pancreatic pseudocyst or abscess, cholestatic liver enzymes with or without jaundice, bile duct stricture, exocrine pancreatic insufficiency, malnutrition, osteoporosis, and peptic ulcer. Pancreatic cancer develops in 5% of patients after 20 years; the risk may relate to tobacco and alcohol use. In patients with hereditary pancreatitis, the risk of pancreatic cancer rises after 50 years of age and reaches 19% by age 70 (see Chapter 39).

Treatment

A. Medical Measures

A low-fat diet should be prescribed. Alcohol is forbidden because it frequently precipitates attacks. Opioids should be avoided if possible. Preferred agents for pain are acetaminophen, NSAIDs, and, if an opioid is necessary, tramadol, along with pain-modifying agents such as tricyclic antidepressants, SSRIs, and gabapentin or pregabalin. Exocrine pancreatic insufficiency is treated with pancreatic enzyme replacement therapy selected based on high lipase activity (Table 16–12). A total dose of at least 40,000 units of lipase in capsules is given with each meal. Doses of 90,000 units or more of lipase per meal may be required in some cases. The tablets should be taken at the start of, during, and at the end of a meal. Concurrent administration of an H_2-receptor antagonist (eg, famotidine, 20 mg orally twice daily), a PPI (eg, omeprazole, 20–60 mg orally daily), or sodium bicarbonate (650 mg orally before and after meals) decreases the inactivation of lipase by acid and may thereby further decrease steatorrhea. In selected cases of alcohol-associated pancreatitis and in cystic fibrosis, enteric-coated microencapsulated preparations may offer an advantage; however, in patients with cystic fibrosis, high-dose pancreatic enzyme replacement therapy has been associated with strictures of the ascending colon. Pain secondary to idiopathic chronic pancreatitis may be alleviated in some cases by pancreatic enzyme replacement therapy (not enteric-coated preparations) or by octreotide, 200 mcg subcutaneously three times daily, although some guidelines recommend against such therapy. Associated diabetes mellitus should be treated (see Chapter 27). Autoimmune pancreatitis is treated with prednisone 40 mg/day orally for 1–2 months, followed by a taper of 5 mg every

Table 16–12. FDA-approved pancreatic enzyme (pancrelipase) preparations.

Product	Enzyme Content/Unit Dose, USP Units		
	Protease	Lipase	Amylase
Immediate-Release Capsules			
Nonenteric-coated			
Viokace 10,440	10,440	39,150	39,150
Viokace 20,880	20,880	78,300	78,300
Delayed-Release Capsules			
Enteric-coated minimicrospheres			
Creon 3000	3000	15,000	9500
Creon 6000	6000	30,000	19,000
Creon 12,000	12,000	60,000	38,000
Creon 24,000	24,000	120,000	76,000
Creon 36,000	36,000	180,000	114,000
Enteric-coated minitablets			
Ultresa 13,800	13,800	27,600	27,600
Ultresa 20,700	20,700	46,000	41,400
Ultresa 23,000	23,000	46,000	41,400
Enteric-coated beads			
Zenpep 3000	3000	16,000	10,000
Zenpep 5000	5000	27,000	17,000
Zenpep 10,000	10,000	55,000	34,000
Zenpep 15,000	15,000	82,000	51,000
Zenpep 20,000	20,000	109,000	68,000
Zenpep 25,000	25,000	136,000	85,000
Enteric-coated microtablets			
Pancreaze 4200	4200	17,500	10,000
Pancreaze 10,500	10,500	43,750	25,000
Pancreaze 16,800	16,800	70,000	40,000
Pancreaze 21,000	21,000	61,000	37,000
Bicarbonate-buffered enteric-coated microspheres			
Pertzye 8000	8000	30,250	28,750
Pertzye + 16,000	16,000	60,500	57,500

USP, US Pharmacopeia.

2–4 weeks. Nonresponse or relapse occurs in 45% of type 1 cases (particularly in those with concomitant IgG_4-associated cholangitis); rituximab is an effective induction and maintenance agent, and azathioprine or long-term low-dose corticosteroid use appears to reduce the risk of relapse.

B. Endoscopic and Surgical Treatment

Endoscopic therapy or surgery may be indicated in chronic pancreatitis to treat underlying biliary tract disease, ensure free flow of bile into the duodenum, drain persistent pseudocysts, treat other complications, eliminate obstruction of the pancreatic duct, attempt to relieve pain, or exclude pancreatic cancer. Liver fibrosis may regress after biliary drainage. Distal bile duct obstruction may be relieved by endoscopic placement of multiple plastic stents or a fully covered self-expandable metal stent in the bile duct. When obstruction of the duodenal end of the pancreatic duct can be demonstrated by ERCP, dilation of or placement of such stents in the duct and pancreatic duct stone lithotripsy or surgical resection of the tail of the pancreas with implantation of the distal end of the duct by pancreaticojejunostomy may be performed. Endoscopic therapy is successful in about 50% of cases. In patients who do not respond to endoscopic therapy, surgery is successful in about 50%. When the pancreatic duct is diffusely dilated, anastomosis between the duct after it is split longitudinally and a defunctionalized limb of jejunum (modified Puestow procedure), in some cases combined with resection of the head of the pancreas (Beger or Frey procedure), is associated with relief of pain in 80% of cases. In advanced cases, subtotal or total pancreatectomy with islet autotransplantation may be considered as a last resort but has variable efficacy and causes pancreatic insufficiency and diabetes mellitus. Endoscopic or surgical (including laparoscopic) drainage is indicated for symptomatic pseudocysts and, in many cases, those over 6 cm in diameter. EUS may facilitate selection of an optimal site for endoscopic drainage. Pancreatic ascites or pancreaticopleural fistulas due to a disrupted pancreatic duct can be managed by endoscopic placement of a stent across the disrupted duct. Pancreatic sphincterotomy or fragmentation of stones in the pancreatic duct by lithotripsy and endoscopic removal of stones from the duct may relieve pain in selected patients. For patients with chronic pain and nondilated ducts, a percutaneous celiac plexus nerve block may be considered under either CT or EUS guidance, with pain relief (albeit often short-lived) in approximately 50% of patients (see Chapter 5). A single session of radiation therapy to the pancreas has been reported to relieve otherwise refractory pain.

Prognosis

Chronic pancreatitis often leads to disability and reduced life expectancy; pancreatic cancer is the main cause of death. The prognosis is best in patients with recurrent acute pancreatitis caused by a remediable condition, such as cholelithiasis, choledocholithiasis, stenosis of the sphincter of Oddi, or hyperparathyroidism, and in those with autoimmune pancreatitis. Medical management of hyperlipidemia, if present, may also prevent recurrent attacks of pancreatitis. The Chronic Pancreatitis Diagnosis Score based on pain, hemoglobin A_{1c} level, C-reactive protein level, BMI, and platelet count has been shown to correlate with hospital admissions and number of hospital days. In alcohol-associated pancreatitis, pain relief is most likely when a dilated pancreatic duct can be decompressed. In patients with disease not amenable to decompressive surgery, addiction to opioids is a frequent outcome of treatment. A poorer quality of life is associated with constant rather than intermittent pain, pain-related disability or unemployment, current smoking, and comorbidities.

When to Refer

All patients with chronic pancreatitis should be referred for diagnostic and therapeutic procedures.

When to Admit

- Severe pain.
- New jaundice.
- New fever.

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Breast Disorders

17

Armando E. Giuliano, MD, FACS, FRCSEd
Sara A. Hurvitz, MD, FACP

BENIGN BREAST DISORDERS

FIBROCYSTIC CONDITION

ESSENTIALS OF DIAGNOSIS

- Painful breast masses; often multiple and bilateral.
- Rapid fluctuation in mass size is common.
- Pain often worsens during premenstrual phase of cycle.
- Most common age is 30–50 years. Rare in postmenopausal women not receiving hormonal replacement.

General Considerations

Fibrocystic condition is the most frequent lesion of the breast. Although commonly referred to as "fibrocystic disease," it does not, in fact, represent a pathologic or anatomic disorder. It is common in women 30–50 years of age but rare in postmenopausal women who are not taking hormonal replacement. Estrogen is considered a causative factor. There may be an increased risk in women who drink alcohol, especially women between 18 and 22 years of age. Fibrocystic condition encompasses a wide variety of benign histologic changes in the breast epithelium, some of which are found so commonly in normal breasts that they are probably variants of normal but have nonetheless been termed a "condition" or "disease."

The microscopic findings of fibrocystic condition include cysts (gross and microscopic), papillomatosis, adenosis, fibrosis, and ductal epithelial hyperplasia. Although it has been thought that a fibrocystic condition increases the risk of breast cancer, *only the variants with a component of epithelial proliferation (especially with atypia), papillomatosis, or increased breast density on mammogram represent true risk factors.*

Clinical Findings

A. Symptoms and Signs

Fibrocystic condition may produce an asymptomatic mass in the breast that is discovered by accident, but pain or tenderness often calls attention to it. Discomfort often occurs or worsens during the premenstrual phase of the cycle, at which time the cysts tend to enlarge. Fluctuations in size and rapid appearance or disappearance of a breast mass are common, as are multiple or bilateral masses and serous nipple discharge. Patients will give a history of a transient lump in the breast or cyclic breast pain.

B. Diagnostic Tests

Mammography and ultrasonography should be used to evaluate a mass in a patient with fibrocystic condition. Ultrasonography alone may be used in women under 30 years of age; mammography may be helpful, but the breast tissue in young women is usually too radiodense to permit a worthwhile study. Ultrasonography is useful in differentiating a cystic mass from a solid mass, especially in women with dense breasts. Simple cysts are not worrisome and require no treatment or follow-up unless they are symptomatic and causing pain, in which case they may be aspirated. Ultrasonography can reliably distinguish fibroadenoma from carcinoma but not from a phyllodes tumor. Because a mass due to fibrocystic condition may nonetheless be difficult to distinguish from carcinoma on the basis of clinical findings and imaging studies, *suspicious lesions should be biopsied.* Core needle biopsy, rather than fine-needle aspiration (FNA), is the preferable technique. If the lesion is cystic, needle aspiration will suffice. Excisional biopsy is rarely necessary but should be done for lesions with atypia or where imaging and biopsy results are discordant. Surgery should be conservative since the primary objective is to exclude cancer. Simple mastectomy or extensive removal of breast tissue is rarely, if ever, indicated for fibrocystic condition.

Differential Diagnosis

Pain, fluctuation in size, and multiplicity of lesions are the features consistent with fibrocystic condition and most helpful in differentiating it from carcinoma. If a dominant mass is present, the diagnosis of cancer should be assumed until disproven by imaging or biopsy. Final diagnosis depends on analysis of a biopsy specimen.

Treatment

When the diagnosis of fibrocystic condition has been established by previous biopsy or is likely because the history is classic, aspiration of a discrete mass suggestive of a cyst is indicated to alleviate pain and, more importantly, to confirm the cystic nature of the mass. The patient is reexamined at intervals thereafter. If no fluid is obtained by aspiration, if fluid is bloody, if a mass persists after aspiration, or if at any time during follow-up a persistent or recurrent mass is noted, biopsy should be performed.

Breast pain associated with generalized fibrocystic condition is best treated by avoiding trauma and by wearing a good supportive brassiere during the night and day. Most hormone therapy is not advisable because it does not cure the condition and has undesirable side effects; danazol (100–200 mg orally twice daily), a synthetic androgen, is the only treatment approved by the US FDA for patients with severe pain. This treatment suppresses pituitary gonadotropins, but androgenic effects (acne, edema, hirsutism) usually make this treatment intolerable; in practice, it is rarely used. Similarly, tamoxifen reduces some symptoms of fibrocystic condition, but because of its side effects, it is not useful for young women unless it is given to reduce the risk of cancer. Postmenopausal women receiving hormone replacement therapy may stop or change doses of hormones to reduce pain. Oil of evening primrose, a natural form of gamolenic acid, has been shown to decrease pain in 44–58% of users. The dosage of gamolenic acid is six capsules of 500 mg orally twice daily. Studies have also demonstrated a low-fat diet or decreasing dietary fat intake may reduce the painful symptoms associated with fibrocystic condition. Topical treatments such as NSAIDs are rarely of value.

The role of caffeine consumption in the development and treatment of fibrocystic condition is controversial. Some studies suggest that eliminating caffeine from the diet is associated with improvement while other studies refute the benefit. Many patients report relief of symptoms after giving up coffee, tea, and chocolate. Similarly, many women find vitamin E (400 IU daily) helpful; however, these observations remain anecdotal.

Prognosis

Exacerbations of pain, tenderness, and cyst formation may occur at any time until menopause, when symptoms usually subside, except in patients receiving hormonal replacement. The patient should be advised to examine her own breasts regularly just after menstruation and to inform her clinician if a mass appears. The risk of breast cancer developing in women with fibrocystic condition with a proliferative or atypical epithelial hyperplasia or papillomatosis is higher than that of the general population. These women should be monitored carefully with physical examinations and imaging studies.

Balci FL et al. Clinical factors affecting the therapeutic efficacy of evening primrose oil on mastalgia. Ann Surg Oncol. 2020; 27:4844. [PMID: 32748152]
Chetlen AL et al. Mastalgia: imaging work-up appropriateness. Acad Radiol. 2017;24:345. [PMID: 27916596]
Osouli Tabrizi S et al. The effect of the herbal medicine on severity of cyclic mastalgia: a systematic review and meta-analysis. J Complement Integr Med. 2021 May 20. [Epub ahead of print] [PMID: 34107571]
Qu P et al. Detection rate is not higher for women with BBD history in breast cancer screening. J Public Health (Oxf). 2021;43:333. [PMID: 31774529]

FIBROADENOMA OF THE BREAST

This common benign neoplasm occurs most frequently in young women, usually within 20 years after puberty. It is somewhat more frequent and tends to occur at an earlier age in Black women. Multiple tumors are found in 10–15% of patients.

The typical **fibroadenoma** is a round or ovoid, rubbery, discrete, relatively movable, nontender mass 1–5 cm in diameter. Clinical diagnosis in young patients is generally not difficult. In women over 30 years, fibrocystic condition of the breast and carcinoma of the breast must be considered. Cysts can be identified by aspiration or ultrasonography. Fibroadenoma does not normally occur after menopause but may occasionally develop after administration of hormones.

No treatment is usually necessary if the diagnosis can be made by core needle biopsy. Excision with pathologic examination of the specimen is performed if the diagnosis is uncertain or the lesion grows significantly. Cryoablation, or freezing of the fibroadenoma, appears to be a safe procedure if the lesion is a biopsy-proven fibroadenoma prior to ablation. Cryoablation is not appropriate for all fibroadenomas because some are too large to freeze or the diagnosis may not be certain. There is no clinical advantage to cryoablation of a histologically proven fibroadenoma beyond the relief that some patients experience when the mass is gone. However, at times a mass of scar or fat necrosis replaces the mass of the fibroadenoma. Reassurance seems preferable to treatment. Distinguishing a large fibroadenoma from a phyllodes tumor based on needle biopsy results or imaging alone is usually not possible; histologic examination after excision is usually required. Presumed fibroadenomas larger than 3–4 cm should be excised to rule out phyllodes tumors.

Phyllodes tumor is a fibroadenoma-like tumor with cellular stroma that grows rapidly. It may reach a large size and, if inadequately excised, will recur locally. The lesion can be benign or malignant. If benign, phyllodes tumor is treated by local excision. The treatment of malignant phyllodes tumor is more controversial, but complete removal of the tumor with a margin of normal tissue avoids recurrence. Because these tumors may be large, total

mastectomy is sometimes necessary. Lymph node dissection is not performed, since the sarcomatous portion of the tumor metastasizes to the lungs and not the lymph nodes.

Erickson LA et al. Fibroadenoma of the breast. Mayo Clin Proc. 2020;95:2573. [PMID: 33153651]
Rayzah M. Phyllodes tumors of the breast: a literature review. Cureus. 2020;12:e10288. [PMID: 32923300]
Tummidi S et al. Fibroadenoma versus phyllodes tumor: a vexing problem revisited! BMC Cancer. 2020;20:648. [PMID: 32660435]

NIPPLE DISCHARGE

In order of decreasing frequency, the following are the most common causes of nipple discharge in the nonlactating breast: duct ectasia, intraductal papilloma, and carcinoma. The important characteristics of the discharge and other factors to be evaluated are listed in Table 17–1.

1. Discharge from a single duct—Spontaneous, unilateral, serous or serosanguineous discharge from a single duct is usually caused by an ectatic duct or an intraductal papilloma or, rarely, by an intraductal cancer. A mass may not be palpable. The involved duct may be identified by pressure at different sites around the nipple at the margin of the areola. Bloody discharge is suggestive of cancer but is more often caused by a benign papilloma in the duct. Cytologic examination may identify malignant cells, but negative findings do not rule out cancer, which is more likely in older women. In any case, the involved bloody duct—and a mass if present—should be excised. A ductogram (a mammogram of a duct after radiopaque dye has been injected), like cytology, is of limited value since excision of the suspicious ductal system is indicated regardless of findings. Ductoscopy, evaluation of the ductal system with a small scope inserted through the nipple, has been attempted but is not effective management.

Table 17–1. Characteristics of nipple discharge in the nonpregnant, nonlactating woman.

Finding	Significance
Serous	Most likely benign FCC, ie, duct ectasia
Bloody	More likely neoplastic–papilloma, carcinoma
Associated mass	More likely neoplastic
Unilateral	Either neoplastic or non-neoplastic
Bilateral	Most likely non-neoplastic
Single duct	More likely neoplastic
Multiple ducts	More likely FCC
Milky	Endocrine disorders, medications
Spontaneous	Either neoplastic or non-neoplastic
Produced by pressure at single site	Either neoplastic or non-neoplastic
Persistent	Either neoplastic or non-neoplastic
Intermittent	Either neoplastic or non-neoplastic
Related to menses	More likely FCC
Premenopausal	More likely FCC
Taking hormones	More likely FCC

FCC, fibrocystic condition.

2. Discharge from multiple ducts—In premenopausal women, spontaneous multiple duct discharge, unilateral or bilateral, most noticeable just before menstruation, is often due to fibrocystic condition. Discharge may be green or brownish. Papillomatosis and ductal ectasia are usually detected only by biopsy. If a mass is present, it should be removed.

A milky discharge from multiple ducts in the nonlactating breast may occur from hyperprolactinemia. Serum prolactin levels should be obtained to search for a pituitary tumor. TSH helps exclude causative hypothyroidism. Numerous antipsychotic medications and other medications may also cause a milky discharge that ceases on discontinuance of the medication.

Oral contraceptive agents or estrogen replacement therapy may cause clear, serous, or milky discharge from a single duct, but multiple duct discharge is more common. In the premenopausal woman, the discharge is more evident just before menstruation and disappears on stopping the medication. If it does not stop, is from a single duct, and is copious, exploration should be performed since this may be a sign of cancer.

A purulent discharge may originate in a subareolar abscess and require removal of the abscess and the related lactiferous sinus.

When localization of the discharge is not possible, no mass is palpable, and the discharge is nonbloody, the patient should be reexamined every 3 or 4 months for a year, and a mammogram and an ultrasound should be performed. Although most discharge is from a benign process, patients may find it annoying or disconcerting. To eliminate the discharge, proximal duct excision can be performed both for treatment and diagnosis.

Çetin K et al. Evaluation and management of pathological nipple discharges without using intraductal imaging methods. Ir J Med Sci. 2020;189:451. [PMID: 31631245]
Gupta D et al. Nipple discharge: current clinical and imaging evaluation. AJR Am J Roentgenol. 2021;216:330. [PMID: 33295815]
Zacharioudakis K et al. Can we see what is invisible? The role of MRI in the evaluation and management of patients with pathological nipple discharge. Breast Cancer Res Treat. 2019;178:115. [PMID: 31352554]

FAT NECROSIS

Fat necrosis is a rare lesion of the breast but is of clinical importance because it produces a mass (often accompanied by skin or nipple retraction) that is usually indistinguishable from carcinoma even with imaging studies. Fat necrosis can occur after trauma; after fat injections to augment breast size or fill defects after breast surgery; and after segmental resection, radiation therapy, or flap reconstruction following mastectomy.

The resultant mass may be confused with cancer. If untreated, the mass gradually disappears. If imaging is not typical of fat necrosis, the safest course is to obtain a biopsy. Core needle biopsy is usually adequate.

Lee J et al. Natural course of fat necrosis after breast reconstruction: a 10-year follow-up study. BMC Cancer. 2021;21:166. [PMID: 33593330]

BREAST ABSCESS

During nursing, an area of redness, tenderness, and induration may develop in the breast. The organism most commonly found in these abscesses is *Staphylococcus aureus* (see Puerperal Mastitis, Chapter 19).

Infection in the nonlactating breast is rare. A subareolar abscess may develop in young or middle-aged women who are not lactating. Often needle or catheter drainage is adequate to treat an abscess, but surgical incision and drainage may be necessary; these infections tend to recur after incision and drainage unless the area is explored during a quiescent interval, with excision of the involved lactiferous duct or ducts at the base of the nipple. In the nonlactating breast, inflammatory carcinoma must always be considered. Thus, incision and biopsy of any indurated tissue with a small piece of erythematous skin is indicated when suspected abscess or cellulitis in the nonlactating breast does not resolve promptly with antibiotics.

Luo J et al. Abscess drainage with or without antibiotics in lactational breast abscess: study protocol for a randomized controlled trial. Infect Drug Resist. 2020;13:183. [PMID: 32021332]
Sugawara C et al. Factors associated with surgical treatment in postpartum women with mastitis or breast abscess: a retrospective cohort study. Breastfeed Med. 2022;17:233. [PMID: 34936486]

DISORDERS OF THE AUGMENTED BREAST

At least 4 million American women have had breast implants. Breast augmentation is performed by placing implants under the pectoralis muscle or, less desirably, in the subcutaneous tissue of the breast. Most implants are made of an outer silicone shell filled with a silicone gel, saline, or some combination of the two. Capsule contraction or scarring around the implant develops in about 15–25% of patients, leading to a firmness and distortion of the breast that can be painful. Some require removal of the implant and surrounding capsule.

Implant rupture may occur in as many as 5–10% of women, and bleeding of gel through the capsule is noted even more commonly. Although silicone gel may be an immunologic stimulant, there is *no increase* in autoimmune disorders in patients with such implants. The FDA has advised symptomatic women with ruptured silicone implants to discuss possible surgical removal with their clinicians. However, women who are asymptomatic and have no evidence of rupture of a silicone gel prosthesis do not require removal of the implant. Women with symptoms of autoimmune illnesses often undergo removal, but no benefit has been shown.

Studies have failed to show any association between implants and an increased incidence of breast cancer. However, breast cancer may develop in a patient with an augmentation prosthesis, as it does in women without them. Detection in patients with implants may be more difficult because mammography is less able to detect early lesions. Mammography is better if the implant is subpectoral rather than subcutaneous. Local recurrence is usually cutaneous or subcutaneous and is easily detected by palpation. Rarely, lymphoma of the breast with silicone implants has been reported.

If a cancer develops in a patient with implants, it should be treated in the same manner as in women without implants. Such women should be offered the option of mastectomy or breast-conserving therapy, which may require removal or replacement of the implant. Radiotherapy of the augmented breast often results in marked capsular contracture. Adjuvant treatments should be given for the same indications as for women who have no implants.

Coroneos CJ et al. US FDA breast implant postapproval studies: long-term outcomes in 99,993 patients. Ann Surg. 2019; 269:30. [PMID: 30222598]
Montemurro P et al. Controllable factors to reduce the rate of complications in primary breast augmentation: a review of the literature. Aesthetic Plast Surg. 2021;45:498. [PMID: 32358668]

CARCINOMA OF THE FEMALE BREAST

ESSENTIALS OF DIAGNOSIS

- Risk factors: Age, nulliparity, childbirth after age 30, family history of breast cancer or deleterious mutations (*BRCA1*, *BRCA2,* or others), and personal history of breast cancer or some types of proliferative conditions.
- Early findings: Mammographic abnormalities and no palpable mass, or single, nontender, firm to hard mass with ill-defined margins.
- Later findings: Skin or nipple retraction; axillary lymphadenopathy; breast enlargement, erythema, edema, pain; fixation of mass to skin or chest wall.

Incidence & Risk Factors

Breast cancer will develop in *one of eight* American women. Next to skin cancer, breast cancer is the most common cancer in women; it is second only to lung cancer as a cause of death. In 2021 there were approximately 281,550 new cases and 43,600 deaths from breast cancer in the United States. Worldwide, breast cancer is diagnosed in approximately 2.3 million women, and about 685,000 die of breast cancer each year.

The most significant risk factor for the development of breast cancer is age. A woman's risk of breast cancer rises

rapidly until her early 60s, peaks in her 70s, and then declines. A significant family history of breast or ovarian cancer imparts a high risk of developing breast cancer. Germline mutations in the *BRCA* family of tumor suppressor genes or other breast cancer susceptibility genes accounts for approximately 5–10% of breast cancer diagnoses and tend to cluster in certain ethnic groups, including women of Ashkenazi Jewish descent. Women with a mutation in the *BRCA1* gene, located on chromosome 17, have an estimated 85% chance of developing breast cancer in their lifetime. Other genes associated with an increased risk of breast and other cancers include *BRCA2* (associated with a gene on chromosome 13); ataxia-telangiectasia mutation (*ATM*), *BARD1, CHEK2, PALB2, RAD51D*; and mutation of the tumor suppressor gene *p53*. Primary care clinicians should assess a woman's personal and family history for breast, ovarian, tubal, or peritoneal cancer (as family history of ovarian and peritoneal cancers increases a woman's risk of breast cancer) using a familial risk assessment tool (eg, https://bcrisktool.cancer.gov/calculator.html). Those with a positive result should receive genetic counseling in order to decide whether genetic testing is indicated.

Even when genetic testing fails to reveal a predisposing genetic mutation, women with a strong family history of breast cancer are at higher risk for development of breast cancer. Compared with a woman with no affected family members, a woman who has one first-degree relative with breast cancer has double the risk of developing breast cancer and a woman with two first-degree relatives with breast cancer has triple the risk of developing breast cancer. The risk is further increased for a woman whose affected family member was premenopausal at the time of diagnosis or had bilateral breast cancer. Lifestyle and reproductive factors also contribute to risk of breast cancer. Nulliparous women and women whose first full-term pregnancy occurred after the age of 30 have an elevated risk. Early menarche (under age 12) and late natural menopause (after age 55) are associated with an increase in risk, especially for hormone receptor–positive (estrogen receptor [ER]-positive or progesterone receptor [PR]-positive or both) breast cancer. Combined oral contraceptive pills also appear to increase the risk of breast cancer, with longer use associated with higher risk. Several studies show that concomitant administration of progesterone and estrogen to postmenopausal women may increase the incidence of breast cancer, compared with the use of estrogen alone or with no hormone replacement treatment. A prior history of chest wall radiation increases the risk of breast cancer years later. Alcohol consumption, high dietary intake of fat, and lack of exercise may also increase the risk of breast cancer. Fibrocystic breast condition is also associated with an increased incidence of cancer only when it is accompanied by proliferative changes, papillomatosis, atypical epithelial hyperplasia, or increased breast density on mammogram. A woman who had cancer in one breast is at increased risk for cancer developing in the other breast. In these women, a contralateral cancer develops at rate of approximately 1% per year. Women with cancer of the uterine corpus have a risk of breast cancer significantly higher than that of the general population, and women with breast cancer have a comparably increased risk of endometrial cancer. Breast cancer tends to be diagnosed more frequently in women of higher socioeconomic status.

Table 17–2. Factors associated with increased risk of breast cancer (listed in alphabetical order).

Age	Older
Family history	Breast cancer in parent, sibling, or child (especially bilateral or premenopausal)
Genetics	*BRCA1*, *BRCA2*, or other unknown mutations
Menstrual history	Early menarche (under age 12) Late menopause (after age 55)
Previous medical history	Endometrial cancer Proliferative forms of fibrocystic disease Cancer in other breast
Race	White
Reproductive history	Nulliparous or late first pregnancy

Women at greater than average risk for developing breast cancer (Table 17–2) should be identified by their clinicians and monitored carefully. Several risk assessment models have been validated to estimate a woman's risk of developing cancer. Women with genetic mutations in whom breast cancer develops may be treated in the same way as women who do not have mutations (ie, lumpectomy), though there is an increased risk of ipsilateral and contralateral breast cancer after lumpectomy for these women.

Bahl M. Management of high-risk breast lesions. Radiol Clin North Am. 2021;59:29. [PMID: 33222998]

Breast Cancer Association Consortium; Dorling L et al. Breast cancer risk genes—association analysis in more than 113,000 women. N Engl J Med. 2021;384:428. [PMID: 33471991]

Daly AA et al. A review of modifiable risk factors in young women for the prevention of breast cancer. Breast Cancer (Dove Med Press). 2021;13:241 [PMID: 33883932]

Jin J. JAMA patient page. Should I be tested for *BRCA* mutations? JAMA. 2019;322:702. [PMID: 31429898]

Kanadys W et al. Use of oral contraceptives as a potential risk factor for breast cancer: a systematic review and meta-analysis of case-control studies up to 2010. Int J Environ Res Public Health. 2021;18:4638. [PMID: 33925599]

Kim G et al. Assessing risk of breast cancer: a review of risk prediction models. J Breast Imaging. 2021;3:144. [PMID: 33778488]

Minami CA et al. Menopausal hormone therapy and long-term breast cancer risk: further data from the Women's Health Initiative Trials. JAMA. 2020;324:347. [PMID: 32720989]

Palmer JR et al. A validated risk prediction model for breast cancer in US Black women. J Clin Oncol. 2021;39:3866. [PMID: 34623926]

Siegel RL et al. Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7. [PMID: 33433946]

Smith SG et al. The impact of body mass index on breast cancer incidence among women at increased risk: an observational study from the International Breast Intervention Studies. Breast Cancer Res Treat. 2021;188:215. [PMID: 33656637]

Tung NM et al. Management of hereditary breast cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. J Clin Oncol. 2020;38:2080. [PMID: 32243226]
US Preventive Services Task Force; Owens DK et al. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2019;322:652. [PMID: 31429903]

Prevention

Multiple clinical trials have evaluated the use of selective ER modulators (SERMs), including tamoxifen and raloxifene, or aromatase inhibitors for prevention of breast cancer in women with no personal history of breast cancer but at high risk for developing the disease. A network meta-analysis of six of these studies including 50,927 women demonstrated a 32% reduction in breast cancer incidence with the use of tamoxifen compared to placebo and a 47% reduction in risk of breast cancer with the use of an aromatase inhibitor compared with placebo. An increased risk of endometrial cancer, cataracts, and venous thromboembolic events has been associated with tamoxifen and a higher rate of fractures and musculoskeletal side effects are associated with aromatase inhibitors. While preventive agents have been shown to be effective at reducing the risk of breast cancer and saving costs, the use of this intervention by women has been relatively low, possibly due to the perceived risks and side effects of therapy.

Some women at high risk may consider prophylactic mastectomy or oophorectomy.

Chlebowski RT et al. Breast cancer prevention: time for a change. JCO Oncol Pract. 2021;17:709. [PMID: 34319769]
Cuzick J et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. Lancet. 2020;395:117. [PMID: 31839281]
Graham D et al. Breast cancer risk-reducing medications. JAMA. 2020;324:310. [PMID: 32692388]
Shieh Y et al. Medications for primary prevention of breast cancer. JAMA. 2020;324:291. [PMID: 32692377]
US Preventive Services Task Force; Owens DK et al. Medication use to reduce risk of breast cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2019;322:857. [PMID: 31479144]

Early Detection of Breast Cancer

A. Screening Programs

Screening detects breast cancer before it has spread to the lymph nodes in about 80% of the women evaluated. This increases the chance of survival to greater than 85% at 5 years.

Substantial evidence supports the use of **routine screening mammography;** however, recommendations relating to timing and frequency vary by different agencies and countries. About one-third of the abnormalities detected on screening mammograms will be found to be malignant when biopsy is performed. The probability of cancer on a screening mammogram is directly related to the Breast Imaging Reporting and Data System (BIRADS) assessment, and workup should be performed based on this classification. The sensitivity of mammography varies from approximately 60% to 90%. This sensitivity depends on several factors, including patient age, breast density, tumor size, tumor histology (lobular versus ductal), location, and mammographic appearance. In young women with dense breasts, mammography is less sensitive than in older women with fatty breasts, in whom mammography can detect at least 90% of malignancies. Smaller tumors, particularly those without calcifications, are more difficult to detect, especially in dense breasts. The lack of sensitivity and the low incidence of breast cancer in young women have led to questions concerning the value of mammography for screening in women 40–50 years of age. The specificity of mammography in women under 50 years varies from about 30% to 40% for nonpalpable mammographic abnormalities to 85% to 90% for clinically evident malignancies. Guidelines from at least six separate organizations exist in the United States and each differs slightly, making it somewhat complex for clinicians and patients to navigate. While the American College of Radiology, American Medical Association, and National Comprehensive Cancer Network (NCCN) recommend starting mammography screening at age 40, the USPSTF recommends starting screening at age 50. Most guidelines recommend annual screening; however, the American Cancer Society recommends decreasing the frequency of screening to every 1–2 years starting at age 55 years and the USPSTF recommends routine mammography be done no more than every 2 years beginning at age 50 years. It is generally agreed that mammography should continue until life expectancy is shorter than 7–10 years, although the USPSTF recommends stopping screening after age 74 years regardless of life expectancy. Thus, clinicians should have an informed discussion with patients about screening mammography regarding its potential risks (eg, false positives, overdiagnosis, radiation exposure) and benefits (eg, early diagnosis), taking into consideration a patient's individual risk factors.

B. Imaging

1. Mammography—Mammography is the most reliable means of detecting breast cancer before a mass can be palpated. Most slowly growing cancers can be identified by mammography at least 2 years before reaching a size detectable by palpation.

Indications for mammography are as follows: (1) screening at regular intervals asymptomatic women at risk for developing breast cancer; (2) evaluating each breast when a diagnosis of potentially curable breast cancer has been made, and at regular intervals thereafter; (3) evaluating a questionable or ill-defined breast mass or other suspicious change in the breast; (4) searching for an occult breast cancer in women with metastatic disease in axillary nodes or elsewhere from an unknown primary; (5) screening women prior to cosmetic operations or prior to biopsy of a mass, to examine for an unsuspected cancer; (6) monitoring women with breast cancer who have been treated with breast-conserving surgery and radiation; and (7) monitoring the contralateral breast in women with breast cancer treated with mastectomy.

Calcifications are the most easily recognized mammographic abnormality. The most common findings associated with carcinoma of the breast are clustered pleomorphic microcalcifications. Such calcifications are usually at least five to eight in number, aggregated in one part of the breast and differing from each other in size and shape, often including branched or V- or Y-shaped configurations. There may be an associated mammographic mass density or, at times, only a mass density with no calcifications. Such a density usually has irregular or ill-defined borders and may lead to architectural distortion within the breast, but may be subtle and difficult to detect.

Patients with a dominant or suspicious mass on examination must undergo biopsy despite mammographic findings. The mammogram should be obtained prior to biopsy so that other suspicious areas can be noted and the contralateral breast can be evaluated. *Mammography is never a substitute for biopsy* because it may not reveal clinical cancer, especially in a very dense breast.

Communication and documentation among the patient, the referring clinician, and the interpreting physician are critical for high-quality screening and diagnostic mammography. The patient should be told about *how* she will receive timely results of her mammogram; that mammography does not "rule out" cancer; and that she may receive a correlative examination such as ultrasound at the mammography facility if referred for a suspicious lesion. She should also be aware of the technique and need for breast compression and that this may be uncomfortable. The mammography facility should be informed in writing by the clinician of abnormal physical examination findings. The Agency for Health Care Policy and Research Clinical Practice Guidelines strongly recommend that all mammography reports be communicated in writing to the patient and referring clinician. Legislation has been passed in a number of US states that requires imaging facilities to report to patients the density of their breasts. This may prompt women with dense breasts to discuss with their clinician whether or not additional screening options would be appropriate in addition to mammogram.

2. Other imaging—MRI and ultrasound may be useful screening modalities in women who are at high risk for breast cancer but not for the general population. The *sensitivity* of MRI is much higher than mammography; however, the *specificity* is significantly lower and this results in multiple unnecessary biopsies. The increased sensitivity despite decreased specificity may be considered a reasonable trade-off for those at increased risk for developing breast cancer but not for normal-risk population. The NCCN guidelines recommend MRI in addition to screening mammography for high-risk women, including those with deleterious mutations, those who have a lifetime risk of breast cancer of at least 20%, and those with a personal history of lobular carcinoma in situ (LCIS).

Women who received radiation therapy to the chest in their teens or twenties are also known to be at high risk for developing breast cancer and screening MRI may be considered in addition to mammography. A Netherlands study (Dense Tissue and Early Breast Neoplasm Screening "DENSE") involving over 40,000 women with extremely dense breast tissue demonstrated that the addition of annual MRI to screening mammography was associated with a lower rate of cancers being diagnosed in 2 years.

Houser M et al. Current and future directions of breast MRI. J Clin Med. 2021;10:5668. [PMID: 34884370]

C. Clinical Breast Examination and Self-Examination

Breast self-examination has *not* been shown to improve survival. Because of the lack of strong evidence demonstrating value, the American Cancer Society no longer recommends monthly breast self-examination. Nonetheless, patients should recognize and report any breast changes to their clinicians as it remains an important facet of proactive care.

Destounis SV et al. Update on breast density, risk estimation, and supplemental screening. AJR Am J Roentgenol. 2020;214:296. [PMID: 31743049]
García-Albéniz X et al. Continuation of annual screening mammography and breast cancer mortality in women older than 70 years. Ann Intern Med. 2020;172:381. [PMID: 32092767]
Harkness EF et al. Risk-based breast cancer screening strategies in women. Best Pract Res Clin Obstet Gynaecol. 2020;65:3. [PMID: 31848103]
Hong S et al. Effect of digital mammography for breast cancer screening: a comparative study of more than 8 million Korean women. Radiology. 2020;294:247. [PMID: 31793847]

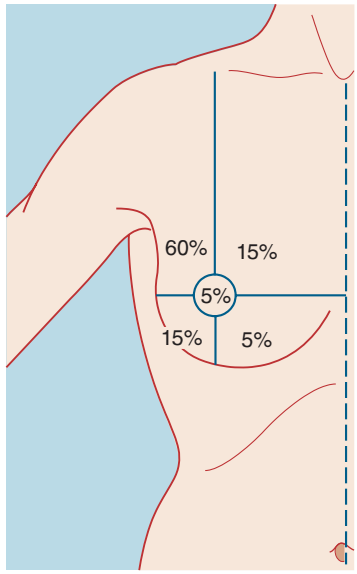
Clinical Findings Associated with Early Detection of Breast Cancer

A. Symptoms and Signs

The presenting complaint in about 70% of patients with breast cancer is a lump (usually painless) in the breast. About 90% of these breast masses are discovered by the patient. Less frequent symptoms are breast pain; nipple discharge; erosion, retraction, enlargement, or itching of the nipple; and redness, generalized hardness, enlargement, or shrinking of the breast. Rarely, an axillary mass or swelling of the arm may be the first symptom. Back or bone pain, jaundice, or weight loss may be the result of systemic metastases, but these symptoms are rarely seen on initial presentation.

The relative frequency of carcinoma in various anatomic sites in the breast is shown in Figure 17–1.

Inspection of the breast is the first step in physical examination and should be carried out with the patient sitting, arms at her sides and then overhead. Abnormal variations in breast size and contour, minimal nipple retraction, and slight edema, redness, or retraction of the skin can be identified (Figure 17–2). Asymmetry of the breasts and retraction or dimpling of the skin can often be accentuated by having the patient raise her arms overhead or press her hands on her hips to contract the pectoralis muscles. Axillary and supraclavicular areas should be thoroughly palpated for enlarged nodes with the patient sitting. Palpation of the breast for masses or other changes should be performed with the patient both seated and supine with the arm abducted. Palpation with a rotary motion of the

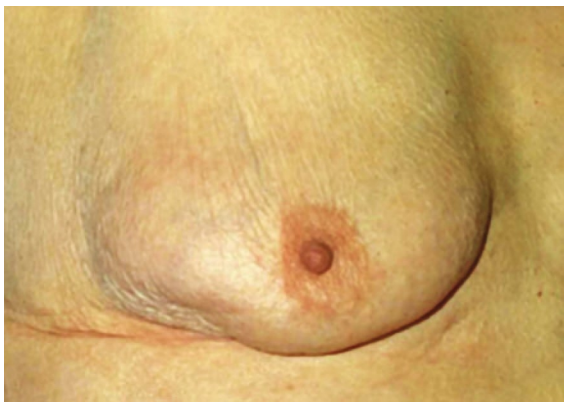


▲ **Figure 17–1.** Frequency of breast carcinoma at various anatomic sites.

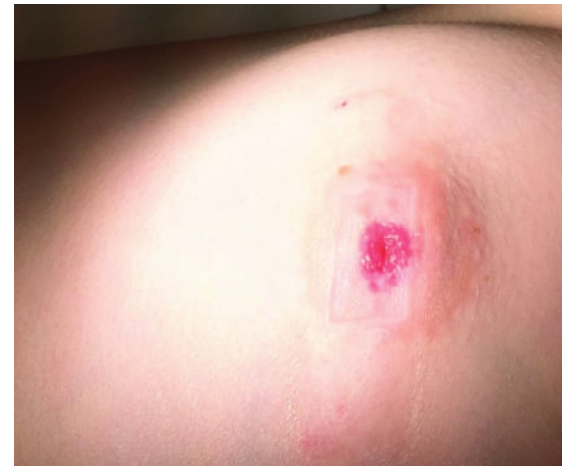
examiner's fingers as well as a horizontal stripping motion has been recommended.

Breast cancer usually consists of a nontender, firm or hard mass with poorly delineated margins (caused by local infiltration). Small (1–2 mm) erosions of the nipple epithelium may be the only manifestation of Paget disease of the breast (Figure 17–3). Watery, serous, or bloody discharge from the nipple is an occasional early sign but is more often associated with benign disease.

A lesion smaller than 1 cm in diameter may be difficult or impossible for the examiner to feel but may be discovered by the patient. The patient should always be asked to demonstrate the location of the mass. If the clinician fails to confirm the patient's suspicions and imaging studies are normal, the examination should be repeated in 2–3 months, preferably 1–2 weeks after the onset of menses. During the premenstrual phase of the cycle, increased innocuous nodularity may suggest neoplasm or may obscure an underlying lesion. If there is any question regarding the nature of an abnormality under these circumstances, the patient should be asked to return after her menses.



▲ **Figure 17–2.** Skin dimpling. (Used, with permission, from Armando E. Giuliano, MD.)



▲ **Figure 17–3.** Paget disease. (Used, with permission, from Armando E. Giuliano, MD.)

Metastases tend to first involve regional lymph nodes, which may be palpable. One or two movable, nontender, not particularly firm axillary lymph nodes 5 mm or less in diameter are frequently present and are generally not significant. Firm or hard nodes larger than 1 cm are typical of metastases. Axillary nodes that are matted or fixed to skin or deep structures indicate advanced disease (at least stage III). If the examiner thinks that the axillary nodes are involved, that impression will be borne out by histologic section in about 85% of cases. The incidence of positive axillary nodes increases with the size of the primary tumor. Noninvasive cancers (in situ) do not metastasize. Metastases in node(s) are present in about 30% of patients with clinically negative nodes.

In most cases, no nodes are palpable in the supraclavicular fossa. Firm or hard nodes of any size in this location or just beneath the clavicle should be biopsied. Ipsilateral supraclavicular or infraclavicular nodes containing cancer indicate that the tumor is in an advanced stage (stage III or IV). Edema of the ipsilateral breast or arm, commonly caused by metastatic infiltration of regional lymphatics, is also a sign of advanced cancer.

B. Laboratory Findings

Liver or bone metastases may be associated with elevation of serum alkaline phosphatase. Hypercalcemia is an occasional important finding in advanced cancer of the breast. Serum tumor markers such as carcinoembryonic antigen and CA 15-3 or CA 27-29 are *not* recommended for diagnosis of early lesions or for routine surveillance for recurrence after a breast cancer diagnosis.

C. Imaging

1. For lesions felt only by the patient—Ultrasonography is often valuable and mammography essential when an area

is felt by the patient to be abnormal but the clinician feels no mass. MRI should not be used to rule out cancer because MRI has a false-negative rate of about 3–5%. Although lower than mammography, this false-negative rate cannot permit safe elimination of the possibility of cancer. False-negative results with imaging are more likely seen in infiltrating lobular carcinomas and ductal carcinoma in situ (DCIS) than invasive ductal carcinoma.

2. For metastatic lesions—For patients with suspicious symptoms or signs (bone pain, abdominal symptoms, elevated liver biochemical tests) or locally advanced disease (clinically abnormal lymph nodes or large primary tumors), staging scans are indicated prior to surgery or systemic therapy. Chest imaging with CT or radiographs may be done to evaluate for pulmonary metastases. Abdominal imaging with CT or ultrasound may be obtained to evaluate for liver metastases. Bone scans using ^{99m}Tc-labeled phosphates or phosphonates are more sensitive than skeletal radiographs in detecting metastatic breast cancer. Bone scanning has not proved to be of clinical value as a routine preoperative test in the absence of symptoms, physical findings, or abnormal alkaline phosphatase or calcium levels. The frequency of abnormal findings on bone scan parallels the status of the axillary lymph nodes on pathologic examination. PET scanning alone or combined with CT (PET-CT) may also be used for detecting soft tissue or visceral metastases in patients with locally advanced disease or with symptoms or signs of metastatic disease.

D. Diagnostic Tests

1. Aspiration—If a tumor is palpable and feels like a cyst, an 18-gauge needle can be used to aspirate the fluid and make the diagnosis of cyst. If a cyst is aspirated and the fluid is nonbloody, it does not have to be examined cytologically. If the mass does not recur, no further diagnostic test is necessary.

2. Biopsy—The diagnosis of breast cancer depends ultimately on examination of tissue or cells removed by biopsy. Treatment should never be undertaken without an unequivocal histologic or cytologic diagnosis of cancer. About 60% of lesions clinically thought to be cancer prove on biopsy to be benign, while about 30% of clinically benign lesions are found to be malignant. These findings demonstrate the fallibility of clinical judgment and the necessity for biopsy. *The safest course is biopsy examination of all suspicious lesions found on physical examination or imaging, or both.*

There is only one probable exception to the need for a histologic diagnosis of a breast mass: a nonsuspicious, presumably fibrocystic mass, in a premenopausal woman. Rather, these masses can be observed through one or two menstrual cycles. However, the mass must be biopsied if it does not completely resolve during this time and ultrasonographic findings show that it is not cystic or benign appearing (like a fibroadenoma or intramammary lymph node). Figures 17–4 and 17–5 present algorithms for management of breast masses in premenopausal and postmenopausal patients.

The simplest biopsy method is needle biopsy, either by aspiration of tumor cells (FNA cytology) or by obtaining a small core of tissue with a hollow needle (core needle biopsy).

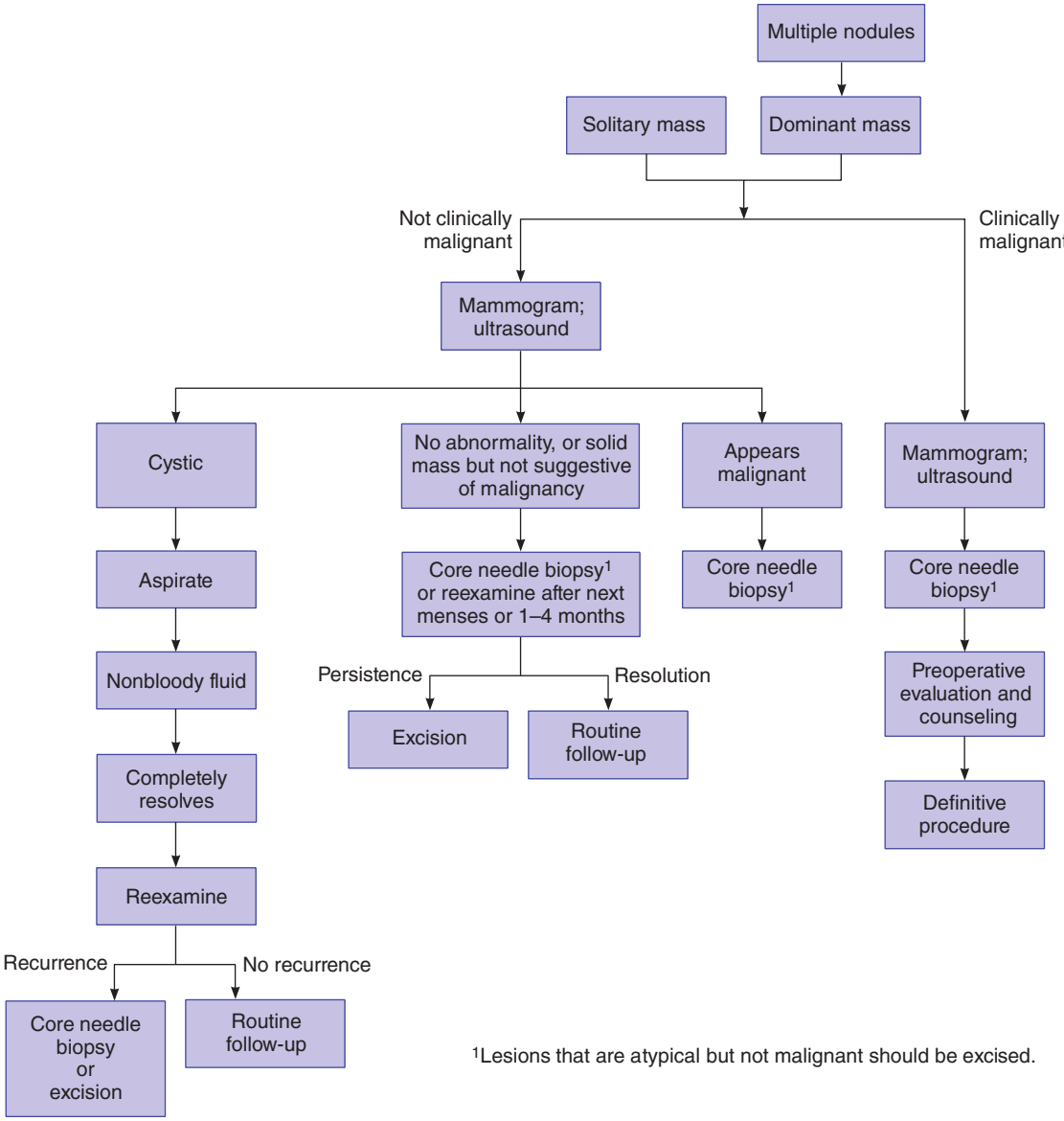
Core (large) needle biopsy removes a core of tissue with a large cutting needle for histologic examination and *is the diagnostic procedure of choice* for both palpable and image-detected abnormalities. Handheld biopsy devices make large-core needle (14-gauge) biopsy of a palpable mass easy and cost effective in the office with local anesthesia. As in the case of any needle biopsy, the main problem is sampling error due to improper positioning of the needle, giving rise to a false-negative test result. This is extremely unusual with image-guided biopsies. Core needle biopsy allows the tumor to be tested for the expression of biological markers, such as ER, PR, and *HER2*.

FNA cytology is a technique whereby cells are aspirated with a small needle and examined cytologically. This technique can be performed easily with virtually no morbidity and is much less expensive than excisional or open biopsy. The main disadvantages are that it requires a pathologist skilled in the cytologic diagnosis of breast cancer and it is subject to sampling problems. Furthermore, noninvasive cancers usually cannot be distinguished from invasive cancers. The incidence of false-positive diagnoses is extremely low, perhaps 1–2%. The false-negative rate is as high as 10%. Most experienced clinicians would not leave a suspicious dominant mass in the breast even when FNA cytology is negative unless the clinical diagnosis, breast imaging studies, and cytologic studies were all in agreement, such as for a fibrocystic lesion or fibroadenoma. Given the stated limitations, *core needle biopsy, rather than FNA, is the modality of choice for sampling an abnormal breast mass.* FNA can be useful for biopsy of suspicious lymph nodes near the axillary vein.

Open biopsy under local anesthesia as a separate procedure prior to deciding upon definitive treatment has become less common with the increased use of core needle biopsy. Core needle biopsy, when positive, offers a more rapid approach with less expense and morbidity, but when nondiagnostic it must be followed by open biopsy. It generally consists of an **excisional biopsy,** which is done through an incision with the intent to remove the entire abnormality, not simply a sample. Intraoperative frozen section examination of a breast biopsy has generally been abandoned unless there is a high clinical suspicion of malignancy in a patient well prepared for the diagnosis of cancer and its treatment options.

3. Biopsy with ultrasound guidance—Ultrasonography may show signs suggestive of carcinoma, such as an irregular mass or a mass within a cyst in the rare case of intracystic carcinoma. Nonpalpable mammographic densities that appear benign should be investigated with ultrasound to determine whether the lesions are cystic or solid or have features suggestive of a malignancy. These may even be needle biopsied with ultrasound guidance.

4. Biopsy with mammographic guidance—When a suspicious abnormality is identified by mammography alone and cannot be palpated by the clinician, the lesion should

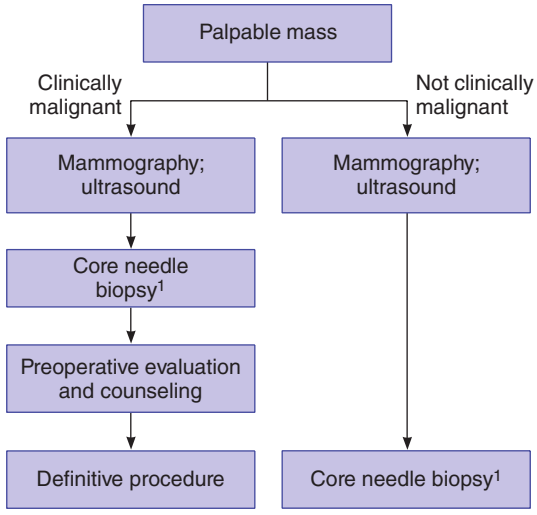


▲ **Figure 17–4. Evaluation of breast masses in premenopausal women.** (Reproduced with permission from Giuliano AE, Srour MK. Breast disease. In: Berek JS, Hacker NF. Berek & Hacker's [editors], *Gynecologic Oncology*. 7th ed. Philadelphia: Wolters Kluwer, 2021.)

be biopsied under mammographic guidance. Mammographic guidance can be used for core needle biopsies or excisional biopsies.

A metal clip should be placed after any image-guided core biopsy to facilitate finding the site of the lesion if subsequent treatment is necessary. Some atypical lesions such as atypical ductal hyperplasia or papilloma may require excision because they are associated with a malignancy in 15–25% of cases.

5. Other imaging modalities—Other modalities of breast imaging have been investigated for diagnostic purposes. Automated breast ultrasonography is useful in distinguishing cystic from solid lesions but should be used only as a supplement to physical examination and mammography. MRI is highly sensitive but not specific and should not be used for screening except in highly selective cases. For example, MRI is useful in differentiating scar from recurrence post-lumpectomy and is valuable to screen high-risk women (eg, women with deleterious mutations). It may also be of value to examine for multicentricity when there is a known primary cancer; to examine the contralateral breast in women with cancer; to examine the extent of cancer, especially lobular carcinomas; or to determine the response to neoadjuvant chemotherapy. Moreover, MRI-detected suspicious findings that are not seen on mammogram or ultrasound may be biopsied under MRI guidance.



▲ **Figure 17–5. Evaluation of breast masses in postmenopausal women.** (Reproduced with permission from Giuliano AE, Srour MK. Breast disease. In: Berek JS, Hacker NF. Berek & Hacker's [editors], *Gynecologic Oncology*. 7th ed. Philadelphia: Wolters Kluwer, 2021.)

PET scanning does not appear useful in evaluating the breast itself but is useful to examine for distant metastases.

6. Cytology—Cytologic examination of nipple discharge or cyst fluid may be helpful on rare occasions. As a rule, mammography (or ductography) and breast biopsy are required when nipple discharge or cyst fluid is bloody or cytologically questionable.

Sutton EJ et al. Accuracy of magnetic resonance imaging-guided biopsy to verify breast cancer pathologic complete response after neoadjuvant chemotherapy: a nonrandomized controlled trial. JAMA Netw Open. 2021;4:e2034045. [PMID: 33449096]

Differential Diagnosis

The most common lesions in the differential diagnosis of breast cancer are the following, in descending order of frequency: fibrocystic condition of the breast, fibroadenoma, intraductal papilloma, lipoma, and fat necrosis.

Staging

The American Joint Committee on Cancer and the International Union Against Cancer have a joint TNM (tumor, regional lymph nodes, distant metastases) staging system for breast cancer (Table 17–3). All patients are assigned an anatomic stage based on TNM. The eighth edition is a landmark change because it adds biologic markers (ER, PR, HER2, histologic grade, and 21-gene Recurrence Score) to modify the anatomic staging. Thus, each patient is assigned not only an anatomic stage but also a prognostic stage, incorporating these biological factors. The *clinical* prognostic stage, in which T, N, M, grade, and HER2 and hormone receptor status are incorporated, is assigned to all breast cancer patients and is the only prognostic staging classification appropriate for patients who receive neoadjuvant (presurgical) systemic therapy or who do not undergo surgery. The *pathologic* prognostic stage is assigned to those patients who undergo surgery as their initial breast cancer treatment. This is based on T, N, M,

Table 17–3. American Joint Commission on Cancer TNM anatomic stage groups.[1]

When T Is…	And N Is…	And M Is…	Then the Stage Group Is[2]…
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

[1]The Anatomic Stage Group table should only be used in global regions where biomarker tests are not routinely available. Cancer registries in the United States must use the prognostic stage group table for case reporting.

[2]T1 includes micrometastases (T1mi). T0 and T1 tumors with lymph node micrometastases only are excluded from stage IIA and are classified as stage IB. M0 includes M0 with isolated tumor cells (i+). The designation pM0 is not valid; any M0 is clinical. If a patient presents with M1 disease before neoadjuvant systemic therapy, then the stage is stage IV and remains stage IV regardless of response to neoadjuvant therapy. Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided the studies are performed within 4 months of diagnosis in the absence of disease progression and provided the patient has not received neoadjuvant therapy. Staging after neoadjuvant therapy is denoted with a "yc" or "yp" prefix to the T and N classification. No stage group is assigned if there is a complete pathological response (pCR) to neoadjuvant therapy: for example, ypT0ypN0cM0.

Reproduced with permission from Giuliano AE et al. Breast cancer – major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(4): 290–303.

Table 17–4. Histologic types of breast cancer.

Type	Frequency of Occurrence
Infiltrating ductal (not otherwise specified)	80–90%
Medullary	5–8%
Colloid (mucinous)	2–4%
Tubular	1–2%
Papillary	1–2%
Invasive lobular	6–8%
Noninvasive	4–6%
Intraductal	2–3%
Lobular in situ	2–3%
Rare cancers	< 1%
Juvenile (secretory)	
Adenoid cystic	
Epidermoid	
Sudoriferous	

grade, HER2, hormone receptor status, and in some patients with small ER-positive, HER2-negative, node-negative tumors, 21-gene recurrence score.

Pathologic Types

Numerous pathologic subtypes of breast cancer can be identified histologically (Table 17–4).

Except for the in situ cancers, the histologic subtypes have only a slight bearing on prognosis when outcomes are compared after accurate staging. The noninvasive cancers by definition are confined by the basement membrane of the ducts and lack the ability to spread. Histologic parameters for invasive cancers, including lymphovascular invasion and tumor grade, have been shown to be of prognostic value. Immunohistochemical analysis for expression of hormone receptors and for overexpression of HER2 in the primary tumor offers prognostic and therapeutic information.

Special Clinical Forms of Breast Cancer

A. Paget Carcinoma

Paget carcinoma is uncommon (about 1% of all breast cancers). Over 85% of cases are associated with an underlying invasive or noninvasive cancer, usually a well-differentiated infiltrating ductal carcinoma or a DCIS. Gross nipple changes are often minimal, and a tumor mass may not be palpable.

Because the nipple changes appear innocuous, the diagnosis is frequently missed. The first symptom is often itching or burning of the nipple, with superficial erosion or ulceration. These are often diagnosed and treated as dermatitis or bacterial infection, leading to delay or failure in detection. The diagnosis is established by biopsy of the area of erosion. When the lesion consists of nipple changes only or an associated DCIS, the incidence of axillary metastases is extremely low, and the prognosis is excellent. When a breast mass or invasive cancer is also present, the incidence of axillary metastases rises, with an associated marked decrease in prospects for cure by surgical or other treatment.

B. Inflammatory Carcinoma

This is the most malignant form of breast cancer and constitutes less than 3% of all cases. The clinical findings consist of a rapidly growing, sometimes painful mass that enlarges the breast. The overlying skin becomes erythematous, edematous, and warm. Often there is no distinct mass since the tumor diffusely infiltrates the involved breast. The inflammatory changes, often mistaken for an infection, are caused by carcinomatous invasion of the subdermal lymphatics, with resulting edema and hyperemia. If the clinician suspects infection but the lesion does not respond to antibiotics within 1–2 weeks, biopsy should be performed. Metastases tend to occur early and widely; while rarely deemed curable in the past, anti-HER2 therapy (if HER2 overexpressing or amplified), surgery, and chemotherapy have resulted in some long-term cures for patients with inflammatory carcinoma. Mastectomy is indicated when chemotherapy and radiation have resulted in clinical remission with no evidence of distant metastases. In these cases, residual disease in the breast may be eradicated. Sentinel node biopsy is not indicated due to the high false-negative rate.

Breast Cancer Occurring During Pregnancy or Lactation

Breast cancer complicates up to one in 3000 pregnancies. Its incidence is increasing as women are having children at an older age. The diagnosis is frequently delayed because physiologic changes in the breast may obscure the lesion and screening mammography is not done in young or pregnant women. Termination of pregnancy has not been shown to improve maternal prognosis. The decision whether to terminate the pregnancy must be made on an individual basis, taking into account the patient's wishes, the clinical stage of the cancer and overall prognosis, the gestational age of the fetus, and the potential for premature ovarian failure in the future with systemic therapy.

It is important for primary care and reproductive specialists to aggressively work up any breast abnormality discovered in a pregnant woman. Pregnancy (or lactation) is not a contraindication to operation or treatment, and therapy should be based on the stage of the disease as in the nonpregnant (or nonlactating) woman. Women with early-stage gestational breast cancer who choose to continue their pregnancy should undergo surgery to remove the tumor and systemic therapy if indicated. Often neoadjuvant systemic therapy may be given during pregnancy and the operation and radiation therapy delayed. Retrospective reviews of patients treated with anthracycline-containing regimens for gestational cancers (including leukemia and lymphomas) have established the relative safety of these regimens during pregnancy for both the patient and the fetus.

Taxane-based and trastuzumab-based regimens have not been evaluated extensively, however. Radiation therapy should be delayed until after delivery.

Bilateral Breast Cancer

Bilateral breast cancer occurs in less than 5% of cases, but there is as high as a 20–25% incidence of later occurrence of cancer in the second breast. Bilaterality occurs more often in familial breast cancer, in women under age 50 years, and when there is a deleterious mutation. The incidence of second breast cancers increases directly with the length of time the patient is alive after her first cancer—about 1–2% per year. Tamoxifen or aromatase inhibitors decrease the risk of a contralateral hormone receptor–positive cancer.

In patients with breast cancer, mammography should be performed before primary treatment and at regular intervals thereafter to search for occult cancer in the opposite breast or conserved ipsilateral breast.

LCIS and Noninvasive Cancer

Noninvasive cancer can occur within the ducts (DCIS) or lobules (LCIS). DCIS tends to be unilateral and is believed to progress to invasive cancer if untreated. Invasive cancer will develop in the same breast in approximately 40–60% of women who have unresected DCIS. In the eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, LCIS is no longer considered a cancer. LCIS is generally agreed to be a marker of an increased risk of breast cancer rather than a direct precursor of breast cancer itself. The probability of breast cancer (DCIS or invasive cancer in either breast) in a woman in whom LCIS has been diagnosed is estimated to be 1% per year. If LCIS is detected on core needle biopsy, an excisional biopsy without lymph node sampling may be performed to rule out DCIS or invasive cancer, but NCCN guidelines suggest observation alone is satisfactory. The incidence of LCIS is rising, likely due to increased use of screening mammography. In addition, the rate of mastectomy after the diagnosis of LCIS is increasing in spite of the fact that mastectomy is only recommended in those patients who otherwise have an increased risk of breast cancer through family history, genetic mutation, or past exposure to thoracic radiation. Pleomorphic LCIS may behave more like DCIS and may be associated with invasive carcinoma. For this reason, pleomorphic LCIS should be surgically removed with clear margins.

The treatment of intraductal lesions is controversial. DCIS can be treated by wide excision with or without radiation therapy or with total mastectomy. Conservative management is advised in patients with small lesions amenable to lumpectomy. Patients in whom LCIS is diagnosed or who have received lumpectomy for DCIS may discuss chemoprevention (with hormonal blockade therapy) with their clinician, which is effective in reducing the risk of invasive breast cancer. Axillary metastases from in situ cancers should not occur unless there is an occult invasive cancer. Because a sentinel lymph node biopsy after mastectomy cannot be performed, it should be performed in a patient undergoing mastectomy for DCIS in case an invasive component is discovered.

Giuliano AE et al. Eighth edition of the AJCC Cancer Staging Manual: breast cancer. Ann Surg Oncol. 2018;25:1783. [PMID: 29671136]

Hester RH et al. Inflammatory breast cancer: early recognition and diagnosis is critical. Am J Obstet Gynecol. 2021;225:392. [PMID: 33845027]

Paris I et al. Pregnancy-associated breast cancer: a multidisciplinary approach. Clin Breast Cancer. 2021;21:e120. [PMID: 32778512]

Sisti A et al. Paget disease of the breast: a national retrospective analysis of the US population. Breast Dis. 2020;39:119. [PMID: 32390594]

Tumor Biomarkers & Gene Expression Profiling

Hormone receptor–positive tumors are ER-positive or PR-positive, or both. Treatment with a hormonally targeted agent (anti-estrogen or anti-ER) is an essential therapy for hormone receptor–positive breast cancer. Hormone receptor–negative cancers do not respond to endocrine treatments. Patients whose tumors are hormone receptor–positive tend to have a more indolent disease course than those whose tumors are hormone receptor–negative.

The *HER2* (*human epidermal growth factor receptor 2*) gene is an oncogene; breast cancer cells that overproduce the *HER2* gene (HER2-amplified or "HER2-positive" cancers) overproduce the growth-promoting protein HER2. HER2-positive breast cancer is generally more aggressive than breast cancer with normal HER2 expression (HER2-negative breast cancer). Targeted therapies that block HER2 have been shown to significantly improve outcomes for patients with HER2-positive disease.

Determining the ER, PR, and HER2 status of the tumor at the time early breast cancer is diagnosed and, if possible, at the time of recurrence is critical, both to gauge a patient's prognosis and to determine the best treatment regimen. In addition to ER, PR, and HER2 status, other important prognostic factors include the rate at which tumor divides (assessed by an immunohistochemical stain for Ki67) and the grade and differentiation of the cells. These markers may be obtained on core biopsy or surgical specimens, but not reliably on FNA cytology. Individually these biomarkers are predictive and thus provide insight to guide appropriate therapy. Moreover, when combined, they provide useful information regarding risk of recurrence and prognosis in the curative setting.

In general, tumors that lack expression of HER2, ER, and PR ("**triple-negative**") have a higher risk of early recurrence and metastases and are associated with a worse survival compared with other types. Neither endocrine therapy nor HER2-targeted agents are useful for this type of breast cancer. Chemotherapy has been the primary treatment option for triple-negative breast cancer. In contrast, patients with early-stage, hormone receptor–positive breast cancer may not benefit from the addition of chemotherapy to hormonally targeted treatments. Several molecular tests have been developed to assess risk of recurrence and to predict which patients are most likely to benefit

from chemotherapy for early-stage disease. Oncotype DX (Genomic Health/Exact Sciences) evaluates the expression of 21 genes relating to ER, HER2, and proliferation in a tumor specimen and categorizes a patient's risk of recurrence (recurrence score) as high, intermediate, or low risk. Patients in low- or intermediate-risk categories do not benefit from chemotherapy, especially when age 50 or over. This test is primarily indicated for ER-positive, lymph node–negative tumors, but results from the RxPONDER trial suggest that postmenopausal women with 1–3 positive lymph nodes with a recurrence score of less than 25 may not benefit from the use of chemotherapy.

MammaPrint (Agendia) is an FDA-approved 70-gene signature assay that is available for evaluating prognosis. This test classifies patients into good and poor prognostic groups to predict clinical outcome and may be used on patients with hormone receptor–positive or hormone receptor–negative breast cancer. ASCO guidelines indicate this assay may be best used to help determine whether chemotherapy may be safely withheld in patients with hormone receptor–positive, HER2-negative, node-positive breast cancer at high clinical risk. ASCO does not recommend using this assay in hormone receptor–negative or HER2-positive breast cancer. The eighth edition of the AJCC staging system incorporates genomic assays to provide a prognostic stage. Patients with low-risk genomic assays may be downstaged from their TNM stage.

Kalinsky K et al. 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. N Engl J Med. 2021;16:2336. [PMID: 34914339]

Liveringhouse CL et al. Genomically guided breast radiation therapy: a review of the current data and future directions. Adv Radiat Oncol. 2021;6:100731. [PMID: 34409215]

Press MF et al. Assessment of ERBB2/HER2 status in HER2-equivocal breast cancers by FISH and 2013/2014 ASCO-CAP guidelines. JAMA Oncol. 2019;5:366. [PMID: 30520947]

Wolff AC et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med. 2018;142:1364. [PMID: 29846104]

Curative Treatment

Most patients with early breast cancer can be cured. Treatment with a curative intent is advised for clinical stage I, II, and III disease (see Table 39–2). Patients with locally advanced (T3, T4) and even inflammatory tumors may be cured with multimodality therapy. When distant metastatic disease (outside the breast or regional lymph nodes) is diagnosed, palliation becomes the goal of therapy. Treatment with palliative intent is appropriate for all patients with stage IV disease and for patients with unresectable local cancers.

A. Choice and Timing of Primary Therapy

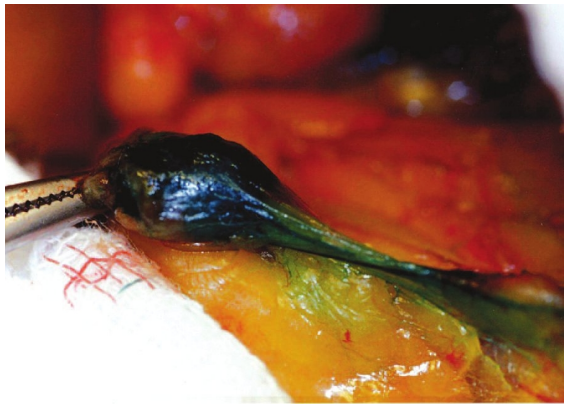
The extent of disease and its biologic aggressiveness are the principal determinants of the outcome of primary therapy. Clinical and pathologic staging help in assessing extent of disease (see Table 17–3), but each is imprecise. Other factors such as tumor grade, hormone receptor assays, *HER2* amplification, and genomic assays are of prognostic and predictive value for benefits from systemic therapy but are not as relevant in determining the type of local therapy. In contrast, the presence of a germline deleterious mutation in *BRCA1* or *BRCA2* may have implications for both local and systemic therapy options; thus, genetic testing of patients with newly diagnosed breast cancer should be considered.

Controversy has surrounded the choice of primary therapy of stage I, II, and III breast carcinoma. Traditionally, the standard of care for stage I, stage II, and most stage III cancer has been surgical resection followed by adjuvant (postoperative) radiation or systemic therapy, or both, when indicated. Administering chemotherapy before surgery (in the neoadjuvant setting) may shrink large tumors, making some patients who require mastectomy candidates for lumpectomy. In addition, the response to neoadjuvant therapy may determine the need for additional postoperative systemic therapy, which may result in improved survival for some tumor types. It is important for patients to understand all the surgical options, including reconstructive options, prior to having surgery. Patients with large primary tumors, inflammatory cancer, or palpably enlarged lymph nodes should have staging scans performed to rule out distant metastatic disease prior to definitive surgery. In general, adjuvant systemic therapy is started when the breast has adequately healed, ideally within 4–8 weeks after surgery. While no prospective studies have defined the appropriate timing of adjuvant chemotherapy, a single-institution study of over 6800 patients suggests that *systemic therapy should be started within 60 days of surgery,* especially in women with stage II or III breast cancer, triple-negative breast cancer, or HER2-positive disease.

B. Surgical Resection

1. Breast-conserving therapy—Multiple, large, randomized studies including the Milan and NSABP trials show that disease-free and overall survival rates are similar for patients with stage I and stage II breast cancer treated with partial mastectomy (breast-conserving lumpectomy or "breast conservation") plus axillary dissection followed by radiation therapy and for those treated by modified radical mastectomy (total mastectomy plus axillary dissection).

Tumor size is a major consideration in determining the feasibility of breast conservation. The NSABP lumpectomy trial randomized patients with tumors as large as 4 cm. To achieve an acceptable cosmetic result, the patient must have a breast of sufficient size to enable excision of a 4-cm tumor without considerable deformity. Therefore, large tumor size is only a relative contraindication. Subareolar tumors, also difficult to excise without deformity, are not contraindications to breast conservation. Oncoplastic techniques combining principles of plastic and reconstructive surgery with surgical oncologic principles are enabling resection of large tumors with excellent cosmetic results. Clinically detectable multifocality is a relative contraindication to breast-conserving surgery, as is fixation to the chest wall or skin or involvement of the nipple or overlying skin.



▲ **Figure 17–6. Sentinel node.** (Used, with permission, from Armando E. Giuliano, MD.)

The patient—not the surgeon—should be the judge of what is cosmetically acceptable. Given the relatively high risk of poor outcome after radiation, concomitant systemic sclerosis (scleroderma) is a contraindication to breast-conserving surgery. A history of prior therapeutic radiation to the ipsilateral breast or chest wall (or both) is also generally a contraindication for breast conservation, although accelerated partial breast irradiation may permit a second breast irradiation.

Axillary dissection is primarily used to properly stage cancer and plan radiation and systemic therapy. Intraoperative lymphatic mapping and sentinel node biopsy identify lymph nodes most likely to harbor metastases if present (Figure 17–6). **Sentinel node biopsy** is a proven alternative to axillary dissection in patients without clinical evidence of axillary lymph node metastases. If sentinel node biopsy reveals no evidence of axillary metastases, it is highly likely that the remaining lymph nodes are free of disease and axillary dissection may be omitted. An important study from the American College of Surgeons Oncology Group randomized women with sentinel node metastases to undergo completion of axillary dissection or to receive no further axillary-specific treatment after lumpectomy; no difference in 10-year survival was found. *Omission of axillary dissection is acceptable for women with tumor-free sentinel nodes or those with involvement of one or two sentinel nodes who are treated with lumpectomy, whole breast irradiation, and adjuvant systemic therapy.*

Breast-conserving surgery with sentinel node biopsy and radiation is the preferred form of treatment for patients with early-stage breast cancer. Despite the numerous randomized trials showing no survival benefit of mastectomy over breast-conserving partial mastectomy with irradiation or of axillary dissection over sentinel node biopsy, these conservative procedures still appear to be underutilized.

2. Mastectomy—Modified radical mastectomy was previously the standard therapy for most patients with early-stage breast cancer. This operation removes the entire breast, overlying skin, nipple, and areolar complex usually with underlying pectoralis fascia with the axillary lymph nodes in continuity. The major advantage of modified radical mastectomy is that radiation therapy may not be necessary, although radiation may be used when lymph nodes are involved with cancer or when the primary tumor is 5 cm or larger. The disadvantage of mastectomy is the cosmetic and psychological impact associated with breast loss. Radical mastectomy, which removes the underlying pectoralis muscle, should be performed rarely, if at all. Axillary node dissection is not indicated for noninvasive cancers because nodal metastases are rarely present. Skin-sparing mastectomies, including those with preservation of the nipple-areolar complex, provide excellent cosmetic and oncologic results; skin-sparing and nipple-sparing mastectomy, however, is not appropriate for all patients. Breast reconstruction, immediate or delayed, should be discussed with patients who choose or require mastectomy. Patients should have an interview with a reconstructive plastic surgeon to discuss options prior to making a decision regarding reconstruction. Time is well spent preoperatively in educating the patient and family about these matters.

C. Radiotherapy

Radiotherapy after breast-conserving surgery consists of 5–7 weeks of radiation for a total dose of 5000–6000 cGy. Most radiation oncologists use a boost dose to the cancer location. Shorter fractionation schedules may be reasonable for women with low-risk, early-stage breast cancer. Guidelines by the American Society of Radiation Oncology and the European Society for Radiotherapy indicate that it is appropriate to discuss partial breast radiation for women over the age of 50 with node-negative, hormone receptor–positive, small (T1) tumors with surgical margins of at least 2 mm. Moreover, in women over the age of 70 with small (less than 2 cm), lymph node–negative, hormone receptor–positive cancers, radiation therapy may be avoided. The recurrence rates after intraoperative radiation, while low, appear significantly higher than postoperative whole breast radiation therapy. However, in all these situations, a balanced discussion with a radiation oncologist to weigh the risks and benefits of each approach is warranted.

Studies suggest that radiotherapy after mastectomy may improve recurrence rates and survival in younger patients and those with tumors 5 cm or larger or positive lymph nodes.

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D. Adjuvant Systemic Therapy

Systemic therapy improves survival and is advocated for most patients with curable breast cancer. In practice, most medical oncologists use chemotherapy for patients with either node-positive or higher-risk (eg, hormone receptor–negative or HER2-positive) node-negative breast cancer and use endocrine therapy for all hormone receptor–positive invasive breast cancer unless contraindicated. Prognostic factors other than nodal status that are used to determine the patient's risks of recurrence are tumor size, ER and PR status, nuclear grade, histologic type, proliferative rate (Ki-67), oncogene expression (Table 17–5), and patient's age and menopausal status. In general, systemic chemotherapy decreases the chance of recurrence by about 30%, hormonal modulation decreases the relative risk of recurrence by 40–50% (for hormone receptor–positive cancer), HER2-targeted therapy decreases the relative risk of recurrence by approximately 40% (for HER2-positive cancer). Systemic chemotherapy is usually given sequentially, rather than concurrently, with radiation. In terms of sequencing, typically chemotherapy is given before radiation and endocrine therapy is started concurrent with or after radiation therapy. Three additional agents became available in 2021 for use in the curative setting for patients with high-risk breast cancer: olaparib, a poly(adenosine diphosphate-ribose) polymerase inhibitor that was shown to reduce the relative risk of an invasive recurrency for *BRCA1/2* carriers with high-risk disease by just over 40%; abemaciclib, a cyclin dependent kinase 4/6 inhibitor shown to improve the invasive disease-free survival for those with high-risk HR-positive disease by approximately 30%; and pembrolizumab, an immune checkpoint inhibitor shown to improve the event-free survival for patients with stage II or greater triple-negative breast cancer by over 35%.

The long-term advantage of systemic therapy is well established. All patients with invasive hormone receptor–positive tumors should consider the use of hormone-modulating therapy. Almost all patients with HER2-positive tumors should receive trastuzumab-containing chemotherapy regimens. In general, adjuvant systemic chemotherapy should not be given to women who have small node-negative breast cancers with favorable histologic findings and tumor biomarkers. The ability to predict more accurately which patients with HER2-negative, hormone receptor–positive, lymph node–negative tumors should receive chemotherapy has improved with the advent of prognostic tools, such as Oncotype DX and MammaPrint (see Biomarkers and Gene Expression Profiling above). These validated tools enable clinicians to better select patients who can safely omit chemotherapy.

Table 17–5. Prognostic factors for recurrence in node-negative breast cancer.

Prognostic Factors	Increased Recurrence	Decreased Recurrence
Size[1]	T3, T2	T1, T0
Hormone receptors (ER, PR)	Negative	Positive
Histologic grade	High	Low
S phase fraction	> 5%	< 5%
Lymphatic or vascular invasion	Present	Absent
HER2 oncogene amplification	High	Low
Epidermal growth factor receptor	High	Low
High Oncotype DX Recurrence Score or other genomic prognostic assays	High score	Low score

ER, estrogen receptor; PR, progesterone receptor.
[1]See Table 17–3 for TNM staging for breast cancer.

1. Chemotherapy—The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis involving over 28,000 women enrolled in 60 trials of adjuvant polychemotherapy versus no chemotherapy demonstrated a significant beneficial impact of chemotherapy on clinical outcome in non–stage IV breast cancer. This study showed that *adjuvant chemotherapy reduces the risk of recurrence and breast cancer–specific mortality in all women and women under the age of 50 derived the greatest benefit.*

A. Anthracycline- and cyclophosphamide-containing regimens—On the basis of the superiority of anthracycline-containing regimens in metastatic breast cancer, both doxorubicin and epirubicin have been studied extensively in the adjuvant setting. Studies comparing Adriamycin (doxorubicin) and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) to cyclophosphamide-methotrexate-5-fluorouracil (CMF) have shown that treatments with anthracycline-containing regimens are at least as effective as treatment with CMF. Retrospective analyses of several studies suggest that anthracyclines may be primarily effective in tumors with HER2 overexpression or alteration in the expression of topoisomerase IIa (the target of anthracyclines and close to the *HER2* gene). Given this, for HER2-negative, node-negative breast cancer, four cycles of AC or six cycles of CMF are probably equally effective.

B. Taxanes—Multiple trials of taxanes (paclitaxel and docetaxel) have been conducted to evaluate their use in combination with anthracycline-based regimens. The majority of these trials showed an improvement in disease-free survival and at least one showed an improvement in overall survival with the taxane-based regimen. A meta-analysis of taxane versus non-taxane anthracycline-based regimen trials showed an improvement in disease-free and overall survival for the taxane-based regimens. Several regimens have been reported including AC followed by paclitaxel (AC-P) or docetaxel (Taxotere) (AC-T), docetaxel concurrent with AC (TAC), 5-fluorouracil-epirubicin-cyclophosphamide (FEC)-docetaxel, and FEC-paclitaxel.

While it is generally agreed that *taxanes should be used for most patients receiving chemotherapy for early breast cancer, data are mounting against the routine use of anthracyclines for HR-positive or HER2-positive disease.* A balanced discussion regarding the potential risks versus benefits of the addition of anthracyclines is warranted, especially in hormone receptor–positive or HER2-positive disease.

c. Duration and dose of chemotherapy—The ideal duration of adjuvant chemotherapy remains uncertain. However, based on the meta-analysis performed in the Oxford Overview (EBCTCG), the current recommendation is for 3–6 months of the commonly used regimens. Data suggest that the timing and sequencing of anthracycline-taxane–based chemotherapy may be important. Multiple trials beginning in the 1980s sought to demonstrate whether dose-intensification of adjuvant chemotherapy by shortening the intervals between cycles ("dose-dense"), or by giving chemotherapy at full dose sequentially rather than concurrently at reduced doses is associated with better outcomes. The EBCTCG meta-analysis included 37,298 patients treated on 26 trials and showed a significant 3.4% absolute decrease and 14% relative risk reduction in breast cancer recurrences with dose-intensification. Moreover, the absolute 10-year breast cancer mortality was improved by 2.4%. While impressive, the benefit of dose-intensification appeared to be strongest in node-positive disease. Its benefit, if any, in HER2-positive disease in the era of HER2-targeted therapy has not been validated. Additionally, the use of dose-intensification in (non-anthracycline) taxane-based regimens has not been evaluated.

d. Chemotherapy side effects—Chemotherapy side effects, which are discussed in Chapter 39, are generally well controlled.

2. Targeted therapy—Targeted therapy refers to agents that are directed specifically against a protein or molecule expressed uniquely on tumor cells or in the tumor microenvironment.

a. HER2 targeted therapy—Approximately 20% of breast cancers are characterized by amplification of the *HER2* oncogene leading to overexpression of the HER2 oncoprotein. The poor prognosis associated with HER2 overexpression has been drastically improved with the development of HER2-targeted therapy. Trastuzumab (Herceptin [H]), a monoclonal antibody that binds to HER2, is effective in combination with chemotherapy (AC-TH or TCH [docetaxel, carboplatin, trastuzumab]) in patients with HER2-overexpressing early breast cancer. Both AC-TH and TCH are FDA-approved for nonmetastatic, HER2-positive breast cancer. In these regimens, trastuzumab is given with chemotherapy and then continued beyond the course of chemotherapy with a goal, in general, to complete a full year. Neoadjuvant chemotherapy plus dual *HER2*-targeted therapy with trastuzumab and pertuzumab (also a HER2-targeted monoclonal antibody that prevents dimerization of HER2 with HER3 and has been shown to be synergistic in combination with trastuzumab) is a standard of care option available to patients with stage II/III HER2-positive breast cancer (see Neoadjuvant Therapy). Adjuvant trastuzumab with pertuzumab is primarily restricted to patients with high-risk, node-positive disease. Neratinib, an orally bioavailable dual HER1 (EGFR), HER2 tyrosine kinase inhibitor, is FDA-approved as extended adjuvant therapy (to be given after completion of 1 year of trastuzumab). The phase 3 placebo-controlled EXTENET study demonstrated that neratinib improves invasive disease-free survival when given for 1 year after completion of a year of standard adjuvant trastuzumab-based therapy (median follow-up 5.2 years, stratified HR 0.73, $P = 0.0083$). The benefit of neratinib appears to be restricted to those with tumor co-expression of ER, PR, or both. Neratinib is associated with GI toxicity, most notably moderate to severe diarrhea in approximately 40% of patients who did not use antidiarrheal prophylaxis. Measures such as starting at a lower dose of neratinib and escalating as tolerated or using prophylactic colestipol or budesonide have been shown to mitigate this side effect.

Patients who undergo neoadjuvant trastuzumab-based chemotherapy and have residual disease remaining at the time of surgery have a comparatively poor outcome compared to those who achieve a pathologic complete response. In the phase 3 randomized KATHERINE trial, 1486 patients with residual disease after standard neoadjuvant trastuzumab/taxane-based therapy (18% of whom also received neoadjuvant pertuzumab) were randomized to receive the antibody-drug conjugate trastuzumab emtansine or standard trastuzumab for 14 cycles after surgery. Patients treated with trastuzumab emtansine had a statistically significantly improved 3-year invasive disease-free survival (88% vs 77%), associated with a 50% relative risk reduction. Adjuvant trastuzumab emtansine is FDA-approved for patients with residual disease after standard trastuzumab-containing neoadjuvant therapy.

Retrospective studies have shown that even small (stage T1a,b) *HER2*-positive tumors have a worse prognosis compared with same-sized *HER2*-negative tumors and may thus be appropriate for trastuzumab-based regimens.

Cardiomyopathy develops in a small but significant percentage (0.4–4%) of patients who receive trastuzumab-based regimens. For this reason, anthracyclines and trastuzumab should not be given concurrently and cardiac function is monitored periodically throughout HER2-targeted therapy.

b. Endocrine therapy—Adjuvant hormone modulation therapy is highly effective in decreasing relative risk of recurrence by 40–50% and mortality by 25% in women with hormone receptor–positive tumors regardless of menopausal status.

(1) Tamoxifen—The traditional 5-year regimen of adjuvant estrogen-receptor antagonist/agonist tamoxifen was compared to a 10-year regimen in the Adjuvant Tamoxifen Longer Against Shorter (ATLAS) trial. Disease-free and overall survival were significantly improved in women who received 10 years of tamoxifen, particularly after year 10. Though these results are impressive, the clinical application of long-term tamoxifen use must be discussed with patients individually, taking into consideration risks of tamoxifen (such as secondary uterine cancers, venous thromboembolic events, and side effects that impact quality of life). Ovarian suppression in addition to tamoxifen has been shown to significantly improve 8-year disease-free survival (83.2% vs 78.9%) and 8-year overall survival (93.3% vs 91.5%) compared to tamoxifen alone in the randomized Suppression of Ovarian Function Trial (SOFT) study, though the benefits appeared to be seen primarily in chemotherapy-treated patients with higher risk disease.

(2) Aromatase inhibitors for postmenopausal women— AIs, including anastrozole, letrozole, and exemestane, reduce estrogen production and are also effective in the adjuvant setting for postmenopausal women. At least seven large randomized trials enrolling more than 24,000 postmenopausal patients with hormone receptor–positive nonmetastatic breast cancer have compared the use of AIs with tamoxifen or placebo as adjuvant therapy. All these studies have shown small but statistically significant improvements in disease-free survival (absolute benefits of 2–6%) with the use of AIs. In addition, AIs have been shown to reduce the risk of contralateral breast cancers and to have fewer associated serious side effects (such as endometrial cancers and thromboembolic events) than tamoxifen. However, they are associated with accelerated bone loss and an increased risk of fractures as well as a musculoskeletal syndrome characterized by arthralgias or myalgias (or both) in the majority of patients. The ASCO and the NCCN have recommended that *postmenopausal women with hormone receptor–positive breast cancer be offered an AI either initially or after tamoxifen therapy.* HER2 status should not affect the use or choice of hormone therapy. In general, AIs are given for 5 years. However, a number of studies are evaluating extended adjuvant therapy for 7–10 years total. The use of extended adjuvant AIs is reserved for high-risk patients after a balanced discussion regarding potential risks versus benefits.

(3) Aromatase inhibitors for premenopausal women— *AIs should not be used in a patient with functioning (premenopausal) ovaries since they do not block ovarian production of estrogen*. However, a combined analysis of the SOFT and Tamoxifen and Exemestane Trial (TEXT) studies showed for the first time that exemestane plus ovarian suppression with triptorelin was associated with a reduced risk of relapse compared to tamoxifen, making this a viable adjuvant therapy option for *premenopausal* women with high-risk ER-positive breast cancers.

c. Bisphosphonates and other bone-modifying agents—Multiple randomized studies have evaluated the use of adjuvant bisphosphonates in addition to standard local and systemic therapy for early-stage breast cancer and have shown, in addition to improvement in bone density, a consistent reduction in the risk of metastatic recurrence in postmenopausal patients. A meta-analysis evaluating more than 18,000 women with early-stage breast cancer treated with bisphosphonates or placebo showed that bisphosphonates reduce the risk of cancer recurrence (especially in bone) and improve breast cancer–specific survival primarily in postmenopausal women. Side effects associated with bisphosphonate therapy include bone pain, fever, osteonecrosis of the jaw (rare, less than 1%), esophagitis or ulcers (for oral bisphosphonates), and kidney injury. The jointly published guidelines of the Cancer Care Ontario and ASCO recommend that bisphosphonate use (zoledronic acid or clodronate) be considered in the adjuvant therapy plan for postmenopausal breast cancer patients. In addition, denosumab, an antibody directed against receptor activator of nuclear factor kappa B ligand (RANK-L), blocks osteoclastic activity. It was evaluated in two phase 3 adjuvant trials with discordant results: The "D-CARE" study randomized patients with early-stage breast cancer (all biologic subtypes) to receive denosumab or placebo and failed to demonstrate a reduction in breast cancer recurrences or deaths. It is speculated that one possible reason for this negative result may be due to the fact that premenopausal patients (who do not have a demonstrated metastatic recurrence benefit from bisphosphonates) were included in the study. In contrast, the ABCSG-18 trial restricted enrollment to postmenopausal women and did show an improvement in disease-free survival with denosumab.

d. Cyclin dependent kinase 4/6 inhibitors—Hormonally driven breast cancer may be particularly sensitive to inhibition of cell cycle regulatory proteins, called cyclin dependent kinases 4 and 6 (CDK 4/6). Three oral CDK4/6 inhibitors are palbociclib, ribociclib, and abemaciclib. In 2021, the FDA approved adjuvant abemaciclib for patients with HR-positive, HER2-negative, node-positive, high-risk breast cancer with a Ki-67 score of at least 20%. Patients who may be candidates for adjuvant abemaciclib thus need their tumor tested for Ki-67 by an FDA-approved immunohistochemical assay.

e. PARP inhibitors—*BRCA*-mutation–associated cancers are deficient in double-strand DNA repair mechanisms and become reliant on an alternative enzyme, poly (adenosine diphosphate-ribose) polymerase (PARP), for DNA repair and survival. Thus, targeting PARP selectively kills breast cancer cells in patients who carry a germline mutation in *BRCA1* or *BRCA2.* Two PARP inhibitors (olaparib and talazoparib) are FDA-approved for the treatment of *BRCA*-associated metastatic breast cancer. The NCCN guidelines include adjuvant olaparib for select patients and recommend germline genetic testing for any patient who may be a candidate for adjuvant olaparib.

While olaparib should be given in combination with standard adjuvant endocrine therapy for HR-positive disease, the use of olaparib in combination with abemaciclib (see above) has not been studied and is not recommended. Thus, if a patient is a candidate for both agents, decisions regarding which agent to use must be made on a case-by-case basis in discussion with the patient. The use of olaparib has also not been studied in combination with capecitabine (see CREATE-X trial below), thus, there are no data to guide selection between these agents in triple-negative *BRCA*-mutation–associated breast cancer with residual disease after neoadjuvant chemotherapy.

3. Adjuvant therapy in older women—Data relating to the optimal use of adjuvant systemic treatment for women over the age of 65 are limited. Results from the EBCTCG overview indicate that while adjuvant chemotherapy yields a smaller benefit for older women compared with younger women, it still improves clinical outcomes. Moreover, individual studies do show that older women with higher risk disease derive benefits from chemotherapy. One study compared the use of oral chemotherapy (capecitabine) to standard chemotherapy in older women and concluded that standard chemotherapy is preferred. Another study (USO TC vs AC) showed that women over the age of 65 derive similar benefits from the taxane-based regimen as

women who are younger. The benefits of endocrine therapy for hormone receptor–positive disease appear to be independent of age. In general, decisions relating to the use of systemic therapy should take into account a patient's comorbidities and physiological age, more so than chronologic age.

E. Neoadjuvant Therapy

The use of systemic therapy prior to resection of the primary tumor (neoadjuvant) is a standard option that should be considered and discussed with patients. This enables the assessment of sensitivity of the tumor to the selected systemic therapy. Patients with hormone receptor–negative, triple-negative, or HER2-positive breast cancer are more likely to have a pathologic complete response (meaning no residual invasive cancer in the breast and sampled nodes at the time of surgery) to neoadjuvant chemotherapy than those with hormone receptor–positive breast cancer. A pathologic complete response at the time of surgery, especially in hormone receptor–negative tumors, is associated with improvement in event-free and overall survival. Neoadjuvant chemotherapy also increases the chance of breast conservation by shrinking the primary tumor in women who would otherwise need mastectomy for local control. Survival after neoadjuvant chemotherapy is similar to that seen with postoperative adjuvant chemotherapy.

1. HER2-positive breast cancer—Dual targeting of HER2 with two monoclonal antibodies, trastuzumab and pertuzumab, showed positive results in two phase 2 clinical trials in the neoadjuvant setting, the TRYPHAENA and the NEOSPHERE studies.

Based on these clinical trials, three regimens are FDA-approved in the HER2-positive neoadjuvant setting: docetaxel (T), cyclophosphamide I, trastuzumab (H), and pertuzumab (P) (TCHP) for six cycles; FEC for three cycles followed by THP for three cycles; or THP for four cycles (followed by three cycles of postoperative FEC). The randomized TRAIN-2 trial compared nine cycles of non-anthracycline, TCHP-type therapy versus FEC-TCHP and demonstrated no improvement in pathologic complete response or event-free survival with the use of anthracycline, thus providing further support for the use of a non-anthracycline regimen for HER2-positive disease. After completing surgery, patients should resume HER2-targeted therapy. If there is residual disease, the standard of care is to give 14 cycles of trastuzumab emtansine based on the KATHERINE trial that showed a significantly improved invasive disease-free survival for patients who received trastuzumab emtansine if they had a non-pathologic complete response to neoadjuvant treatment. In the case of pathologic complete response, trastuzumab with (ie, if node-positive) or without pertuzumab is given to complete 1 year of total therapy with consideration for the use of neratinib as extended adjuvant therapy for high-risk (lymph node–positive, hormone receptor–positive) disease.

2. Hormone receptor–positive, HER2-negative breast cancer—Patients with hormone receptor–positive breast cancer have a lower chance of achieving a pathologic complete response with neoadjuvant therapy than those patients with triple-negative or HER2-positive breast cancers. Studies indicate similar clinical response rates with neoadjuvant endocrine therapy compared to neoadjuvant chemotherapy. Typically, responses are not appreciated unless 4–6 or more months of therapy are given. Outside of the clinical trial setting, the use of neoadjuvant hormonal therapy is generally restricted to postmenopausal patients who are unable or unwilling to tolerate chemotherapy.

3. Triple-negative breast cancer—Recent studies have showed that targeted therapy demonstrated meaningful improvements in long-term outcomes for patients with curable breast cancer that is lacking in *HER2* amplification or hormone receptor expression. A meta-analysis of nine randomized trials including over 2100 patients and a median follow-up of 47–67 months demonstrated not only an improved pathologic complete response rate with the addition of platinum to chemotherapy but also a significantly improved event-free survival and a trend toward improved overall survival.

The anti-PD-1 immune checkpoint inhibitor pembrolizumab was FDA-approved in 2021 for treatment of triple-negative breast cancer in the neoadjuvant setting in combination with chemotherapy, followed by adjuvant pembrolizumab to complete a year. Patients treated with neoadjuvant or adjuvant pembrolizumab should receive it in combination with the taxane, platinum, anthracycline–based regimen. It is not clear whether use of pembrolizumab solely in the adjuvant setting (without use in neoadjuvant setting) benefits patients; thus, it is not recommended.

Questions remain regarding optimal adjuvant treatment of patients with residual disease after neoadjuvant therapy. A standard option based on the CREATE-X study is to use eight cycles of adjuvant capecitabine after neoadjuvant therapy. It is not known whether adding capecitabine to adjuvant pembrolizumab benefits patients who have received neoadjuvant pembrolizumab plus chemotherapy and have residual disease at the time of definitive breast surgery; the combined use of these two agents is not the standard of care. For patients with a *BRCA1* or *BRCA2* mutation and residual triple-negative breast cancer at the time of definitive breast surgery, the use of adjuvant olaparib is an option. However, the combination or sequencing of olaparib and pembrolizumab is untested in this setting.

4. Timing of sentinel lymph node biopsy in neoadjuvant setting—There is considerable concern about the timing of sentinel lymph node biopsy, since the chemotherapy may affect cancer present in the lymph nodes. Several studies have shown that sentinel node biopsy can be done after neoadjuvant therapy. However, a large multicenter study, ACOSOG 1071, demonstrated a false-negative rate of 10.7% when the sentinel lymph node biopsy was performed after neoadjuvant therapy, while the false-negative rate before neoadjuvant therapy is less than 1–5%. The SENTINA trial showed similarly poor results for sentinel node biopsy after neoadjuvant therapy. The false-negative rate falls to an acceptable level if three nodes are removed and isotope and dye are used. Some physicians recommend performing sentinel lymph node biopsy before

administering the chemotherapy in order to avoid a false-negative result and to aid in planning subsequent radiation therapy. Others prefer to perform sentinel lymph node biopsy after neoadjuvant therapy to avoid a second operation and assess post-chemotherapy nodal status. An effective approach for sentinel node biopsy for patients who had involved nodes pre-chemotherapy is to place a clip in the positive node and be sure to excise it at the time of sentinel node biopsy. Important questions remain to be answered involving the use of neoadjuvant therapy, including which neoadjuvant agents to use, duration of treatment, and additional postoperative therapy.

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Palliative Treatment

Palliative treatments are aimed to manage symptoms, improve quality of life, and even prolong survival, without the expectation of achieving cure. Even when cure of the disease is not expected, palliative treatments are appropriate for breast cancer metastatic to distant sites. In the United States, it is uncommon to have distant metastases at the time of diagnosis (de novo metastases). However, most patients who have a breast cancer recurrence after initial local and adjuvant therapy have metastatic rather than local (in breast) disease. Breast cancer most commonly metastasizes to the liver, lungs, and bone, causing symptoms such as fatigue, change in appetite, abdominal pain, cough, dyspnea, or bone pain. Headaches, imbalance, vision changes, vertigo, and other neurologic symptoms may be signs of brain metastases. Triple-negative (ER-, PR-, HER2-negative) and HER2-positive tumors have a higher rate of brain metastases than hormone receptor–positive, HER2-negative tumors.

A. Radiotherapy and Bisphosphonates

Palliative radiotherapy may be advised for primary treatment of locally advanced cancers with distant metastases to control ulceration, pain, and other manifestations in the breast and regional nodes. Irradiation of the breast and chest wall and the axillary, internal mammary, and supraclavicular nodes should be undertaken in an attempt to cure locally advanced and inoperable lesions when there is no evidence of distant metastases. A small number of patients in this group are cured in spite of extensive breast and regional node involvement.

Palliative irradiation is of value also in the treatment of certain bone or soft tissue metastases to control pain or avoid fracture. Radiotherapy is especially useful in the treatment of isolated bony metastases, chest wall recurrences, and brain metastases and, sometimes, in lieu of the preferred option of orthopedic surgery for acute spinal cord compression.

In addition to radiotherapy, bisphosphonate therapy has shown excellent results in delaying and reducing skeletal events in women with bony metastases. Pamidronate and zoledronic acid are FDA-approved intravenous bisphosphonates given for bone metastases or hypercalcemia of malignancy from breast cancer. Denosumab is FDA-approved for the treatment of bone metastases from breast cancer, with data showing that it reduced the time to first skeletal-related event (eg, pathologic fracture) compared to zoledronic acid.

Caution should be exercised when combining radiation therapy with chemotherapy because toxicity of either or both may be augmented by their concurrent administration. In general, *only one type of therapy should be given at a time* unless it is necessary to irradiate a destructive lesion of weight-bearing bone while the patient is receiving chemotherapy. Systemic therapy should be changed only if the disease is clearly progressing or if intolerable side effects have developed. This is especially difficult to determine for patients with destructive bone metastases, since changes in the status of these lesions are difficult to determine radiographically.

B. Targeted Therapy

1. Hormonally based therapy for metastatic disease— The following therapies have all been shown to be effective in hormone receptor–positive metastatic breast cancer: administration of medications that block or downregulate ERs (such as tamoxifen or fulvestrant, respectively) or medications that block the synthesis of hormones (such as AIs); ablation of the ovaries, adrenal, or pituitary glands; and the administration of hormones (eg, estrogens, androgens, progestins); see Table 17–6. Because only 5–10% of

Table 17–6. Hormonally targeted agents commonly used for management of metastatic breast cancer (listed in alphabetical order).

Medications	Action	Dose, Route, Frequency	Major Side Effects
Anastrozole (Arimidex)	AI	1 mg orally daily	Hot flushes, skin rashes, nausea and vomiting, bone loss
Exemestane (Aromasin)	AI	25 mg orally daily	Hot flushes, increased arthralgia/arthritis, myalgia, bone loss
Fulvestrant (Faslodex)	Steroidal estrogen receptor antagonist	500 mg intramuscularly days 1, 15, 29 and then monthly	GI upset, headache, back pain, hot flushes, pharyngitis, injection site pain
Goserelin (Zoladex)	Synthetic LH-releasing analog	3.6 mg subcutaneously monthly	Arthralgias, blood pressure changes, hot flushes, headaches, vaginal dryness, bone loss
Letrozole (Femara)	AI	2.5 mg orally daily	Hot flushes, arthralgia/arthritis, myalgia, bone loss
Leuprolid (Lupron)	Synthetic LH-releasing analog	3.75 or 7.5 mg subcutaneously monthly	Arthralgias, blood pressure changes, hot flushes, headaches, vaginal dryness, bone loss
Megestrol acetate (Megace)	Progestin	40 mg orally four times daily	Fluid retention, venous thromboembolic events; rarely used except in late stage, treatment-refractory disease
Tamoxifen citrate (Nolvadex)	SERM	20 mg orally daily	Hot flushes, uterine bleeding, thrombophlebitis, rash
Toremifene citrate (Fareston)	SERM	60 mg orally daily	Hot flushes, sweating, nausea, vaginal discharge, dry eyes, dizziness

AI, aromatase inhibitor; SERM, selective estrogen receptor modulator.

women with ER-negative tumors respond, they should not receive endocrine therapy. Women within 1 year of their last menstrual period are arbitrarily considered to be premenopausal and should have surgical (bilateral oophorectomy) or chemical ovarian ablation (using a gonadotropin-releasing hormone [GnRH] analog such as leuprolide [Lupron], goserelin [Zoladex], or triptorelin). Premenopausal women who have had chemical or surgical ovarian ablation are then eligible to receive the same hormonally targeted therapies that are available to postmenopausal women. Guidelines indicate that sequential hormonal therapy (Table 17–6) is the preferred treatment for hormone receptor–positive metastatic breast cancer except in the rare case when disease is immediately threatening visceral organs.

A. First-line treatment options—

(1) Hormonally targeted agents—Single-agent hormonally targeted therapy options include the pure ER degrader/antagonist fulvestrant (500 mg intramuscularly days 1 and 15, then every month), tamoxifen (20 mg orally daily), or an AI (anastrozole, letrozole, or exemestane; all oral daily). The average time to disease progression associated with single-agent first-line tamoxifen is 5–8 months and with AI is approximately 8–12 months. The side effect profile of AIs differs from tamoxifen. The main side effects of tamoxifen are nausea, skin rash, and hot flushes. Rarely, tamoxifen induces hypercalcemia in patients with bony metastases. Tamoxifen also increases the risk of venous thromboembolic events and uterine hyperplasia and cancer. The main side effects of AIs include hot flushes, vaginal dryness, and joint stiffness; however, osteoporosis and bone fractures are significantly higher than with tamoxifen. Results from the phase 3 FALCON study (comparing first-line treatment with fulvestrant to anastrozole) showed that the use of first-line fulvestrant significantly improves progression-free survival by almost 3 months with the largest treatment effect observed in patients without visceral disease.

(2) Hormonally targeted therapy plus cyclin dependent kinase inhibition—Hormonally driven breast cancer is particularly sensitive to inhibition of cell cycle regulatory proteins, called cyclin dependent kinases 4 and 6 (CDK 4/6). Studies of three CDK4/6 inhibitors (palbociclib 125 mg daily, ribociclib 600 mg daily, and abemaciclib 150 mg twice daily) combined with an endocrine agent (AI or fulvestrant) all demonstrated a median progression-free survival of over 2 years; the longest median progression-free survival reported in metastatic ER-positive breast cancer to date. Similar progression-free survival benefits were achieved with ribociclib in younger women in the phase 3 randomized trial (MONALEESA-7) that exclusively enrolled premenopausal women (treated with goserelin to suppress ovarian function in combination with endocrine therapy). **Collectively, clinical trials support the use of a CDK4/6 inhibitor plus an AI as the gold standard treatment in the first-line setting of hormone-receptor–positive metastatic breast cancer**. Importantly, these therapies yield objective response rates as good as or better than that seen with chemotherapy. All three CDK inhibitors are FDA-approved in the first-line setting in combination with endocrine therapy. Thus far, ribociclib is the only CDK4/6 inhibitor to report an overall survival benefit (in MONALEESA-2, MONALEESA-3, and MONALEESA-7) when added to endocrine therapy in patients

who previously have not received endocrine therapy for metastatic disease (first-line setting). In general, CDK4/6 inhibitors are well tolerated, though monitoring patients for neutropenia (especially with ribociclib and palbociclib) and management of diarrhea (especially with abemaciclib) are necessary. Febrile neutropenia and infections are rare, and use of growth factors is not required; however, palbociclib and ribociclib are given for 3 consecutive weeks, stopping for 1 week to allow white cell count to recover. Abemaciclib is given twice daily continuously (28-day cycles).

B. Treatment Options When Disease Progresses After Hormonal-Based Therapy—

(1) Fulvestrant plus CDK4/6 inhibitor—Palbociclib, ribociclib, and abemaciclib have been evaluated in phase 3 trials (PALOMA-3, MONALEESA-3, MONARCH-2, respectively) in patients whose disease has progressed on prior endocrine therapy. All three have shown a significant improvement in median progression-free survival; ribociclib and abemaciclib have shown a significant improvement in overall survival when added to fulvestrant. Palbociclib, ribociclib, and abemaciclib are FDA-approved in combination with fulvestrant for this indication and are **the gold standard second-line regimen in patients who have not received a CDK4/6 inhibitor in the first-line setting.** Abemaciclib is also FDA-approved as a single agent (200 mg orally twice daily) for patients with advanced ER-positive breast cancer who have received prior endocrine therapy and chemotherapy. At this time, use of any CDK4/6 inhibitor after disease progression on a CDK4/6 inhibitor is not appropriate outside of a clinical trial.

(2) Secondary or tertiary hormonal therapy—Patients who have disease progression following first-line endocrine-based therapy may be offered a different form of endocrine therapy. For example, if a patient has been treated with an AI as first-line therapy, fulvestrant or tamoxifen should be considered at the time of disease progression as second-line therapy.

(3) Everolimus plus endocrine therapy—Everolimus (Afinitor) is an oral inhibitor of the mammalian target of rapamycin (MTOR)—a protein whose activation has been associated with the development of endocrine resistance. A phase 3, placebo-controlled trial (BOLERO-2) evaluated the AI exemestane with or without everolimus in 724 patients with AI-resistant, hormone receptor–positive metastatic breast cancer and found that patients treated with everolimus had a significantly improved progression-free survival (7.8 months vs 3.2 months) but no significant difference in overall survival. Everolimus has also been evaluated in combination with fulvestrant and shown to have similar improvements in progression-free survival compared to single-agent fulvestrant. The main side effect of everolimus is stomatitis (mouth sores). This can be avoided, almost completely, by the prophylactic use of oral steroid mouthwash starting with cycle 1.

(4) Phosphatidylinositol-3-kinase (PI3K) inhibitors plus endocrine therapy—Approximately 40% of hormone receptor–positive breast cancers have activation of the PI3K-AKT-mTOR pathway, most commonly due to an activating mutation of PI3K on the *PIK3CA* gene. Alpelisib is an oral alpha-isoform selective inhibitor of PI3K with clinical activity in *PIK3CA*-mutated breast cancer. Alpelisib is FDA-approved for *PIK3CA*-mutated hormone receptor–positive breast cancer. Side effects of alpelisib include hyperglycemia, diarrhea, rash, and transaminitis.

2. HER2-targeted agents—For patients with HER2-positive tumors, trastuzumab plus chemotherapy significantly improves clinical outcomes, including survival compared to chemotherapy alone. Pertuzumab is an FDA-approved monoclonal antibody that targets the extracellular domain of *HER2* at a different epitope than targeted by trastuzumab and inhibits receptor dimerization. Treatment with the combination of pertuzumab, trastuzumab, and docetaxel imparts a significantly longer progression-free and overall survival compared with treatment with docetaxel and trastuzumab **and is the first-line gold standard for HER2-positive metastatic breast cancer.** Trastuzumab emtansine had been the second-line gold standard for HER2-positive metastatic breast cancer. In 2021, the FDA-approved antibody-drug conjugate, trastuzumab deruxtecan (T-DXd), replaced T-DM1 as the second-line gold standard (after trastuzumab and taxane-based therapy).

In addition to pertuzumab, trastuzumab, trastuzumab emtansine, and trastuzumab deruxtecan, four other HER2-targeted therapies are FDA-approved for patients who have received two or more prior lines of therapy for advanced-stage disease. A novel HER2-selective oral tyrosine kinase inhibitor, tucatinib, penetrates the blood-brain barrier, potentially improving outcomes for those with brain metastases from breast cancer. A large, randomized trial (HER2CLIMB) compared capecitabine plus trastuzumab plus either tucatinib or placebo in patients with pretreated, HER2-positive advanced disease and demonstrated an improved progression-free survival in the overall population, improved progression-free survival in those with CNS metastases, and importantly, a significantly improved overall survival. Other agents are neratinib (in combination with capecitabine), lapatinib (in combination with capecitabine or trastuzumab), and margetuximab, a monoclonal antibody similar to trastuzumab that is designed to improve the antibody-dependent cellular cytotoxicity mechanism of action when used with chemotherapy.

3. Targeting triple-negative breast cancer—Breast cancers lacking expression of the hormone receptors ER and PR and without overexpression of HER2 behave more aggressively and have traditionally been amenable only to therapy with cytotoxic chemotherapy. However, data supporting the use of immune modulation in the treatment of breast cancer have been practice-changing. PD-L1 is a protein on cancer cell surfaces (as well as other cells) that couples with T cells. This coupling, or immune checkpoint, protects the cancer cells from being destroyed by T cells. Checkpoint inhibitor drugs prevent the PD-1/PD-L1 coupling from taking place, thus allowing the T cells to attack the tumor. A PD-1-targeted immune checkpoint inhibitor, pembrolizumab, is FDA-approved for patients with PD-L1-positive disease in combination with chemotherapy (taxane or gemcitabine/carboplatin) based on results from the KEYNOTE 355 trial. Another FDA-approved therapy for triple-negative disease is sacituzumab govitecan, an

antibody-drug conjugate that delivers SN-38 (active metabolite of the chemotherapy irinotecan) to Trop-2 overexpressing breast cancer cells.

4. Targeting PARP in *BRCA1/2* mutation–associated breast cancer—Poly (adenosine diphosphate-ribose) polymerase (PARP) is an enzyme important in single-strand DNA repair. Patients who carry germline mutations in *BRCA1* or *BRCA2* have tumors with deficient double-strand DNA repair mechanisms. Experts have theorized that inhibiting PARP selectively kills *BRCA1/2*-mutated cancers. A phase 3 clinical trial (OlympiAD) that compared olaparib (an oral PARP inhibitor) to treatment of physician's choice (single-agent chemotherapy) demonstrated a significantly improved progression-free survival (7.0 months vs 4.2 months), an improved response rate, and a lower rate of adverse events than standard therapy. Talazoparib, a second PARP inhibitor, has also been shown to improve outcomes similarly in the phase 3 EMBRACA study. Both olaparib and talazoparib are FDA-approved for *BRCA*-mutated metastatic breast cancer as single agents.

C. Palliative Chemotherapy

Cytotoxic medications should be considered for the treatment of metastatic breast cancer (1) if life- or organ-threatening visceral metastases are present (especially brain, liver, or lymphangitic pulmonary), (2) if hormonal treatment is unsuccessful or the disease has progressed after an initial response to hormonal manipulation (for hormone receptor–positive breast cancer), or (3) if the tumor is ER-negative or HER2-positive. Prior adjuvant chemotherapy does not seem to alter response rates in patients who relapse. A number of chemotherapy medications (including vinorelbine, paclitaxel, docetaxel, gemcitabine, ixabepilone, carboplatin, cisplatin, capecitabine, albumin-bound paclitaxel, eribulin, and liposomal doxorubicin) may be used as single agents with first-line objective response rates ranging from 30% to 50%.

Combination chemotherapy yields statistically significantly higher response rates and progression-free survival rates compared with sequential single-agent therapy but has not been conclusively shown to improve overall survival rates. Combinations that have been tested in phase 3 studies and have proven efficacy compared with single-agent therapy include capecitabine/docetaxel, gemcitabine/paclitaxel, and capecitabine/ixabepilone (see Tables 39–3 and 39–13). It is generally appropriate to treat willing patients with multiple sequential lines of therapy as long as they tolerate the treatment and as long as their performance status is good (eg, at least ambulatory and able to care for self, up out of bed more than 50% of waking hours).

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Prognosis

Stage of breast cancer is the most reliable indicator of prognosis (Tables 17-3 and 17–7). Axillary lymph node status is the best-analyzed prognostic factor and correlates with survival at all tumor sizes. When cancer is localized to the breast

Table 17–7. Approximate survival of patients with breast cancer by TNM stage.

TNM Stage	5 Years	10 Years
0	95%	90%
I	85%	70%
IIA	70%	50%
IIB	60%	40%
IIIA	55%	30%
IIIB	30%	20%
IV	5–10%	2%
All	65%	30%

with no evidence of regional spread after pathologic examination, the clinical cure rate with most accepted methods of therapy is 75% to more than 90%. In fact, patients with small mammographically detected biologically favorable tumors and no evidence of axillary spread have a 5-year survival rate greater than 95%. When the axillary lymph nodes are involved with tumor, the survival rate drops to 50–70% at 5 years and probably around 25–40% at 10 years. The use of biologic markers, such as ER, PR, grade, and HER2, helps identify high-risk tumor types as well as direct treatment used (see Biomarkers & Gene Expression Profiling). Gene analysis studies can predict disease-free survival for some subsets of patients. The eighth edition of the AJCC Staging Manual has incorporated these factors into staging, resulting in incorporation of biologic factors to predict outcome.

Five-year statistics do not accurately reflect the final outcome of therapy. The mortality rate of breast cancer patients exceeds that of age-matched normal controls for nearly 20 years. Thereafter, the mortality rates are equal, though deaths that occur among breast cancer patients are often directly the result of tumor.

In general, breast cancer appears to be somewhat more aggressive and associated with worse outcomes in younger than in older women, and this may be related to the fact that fewer younger women have ER-positive tumors. Disparities in treatment outcome for different racial and ethnic backgrounds have been reported by several studies. These differences appear to be not only due to different socioeconomic factors (and a resulting difference in access to health care) but also due to differences in the subtype of breast cancer diagnosed.

For those patients whose disease progresses despite treatment, some studies suggest supportive group therapy may improve survival. Especially as they approach the end of life, such patients will require meticulous palliative care (see Chapter 5).

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Follow-Up Care

After primary therapy, patients with breast cancer should be monitored long term in order to detect recurrences and to observe the opposite breast for a second primary carcinoma. Local and distant recurrences occur most frequently within the first 2–5 years, especially for hormone receptor–negative tumors. During the first 2 years, most patients should be examined every 6 months, then annually thereafter. Special attention is paid to the contralateral breast because a new primary breast malignancy will develop in 20–25% of patients. In some cases, especially in hormone receptor–positive breast cancer, metastases are dormant for long periods and may appear 20 years or longer after removal of the primary tumor. Although studies have failed to show an adverse effect of hormonal replacement in disease-free patients, it is rarely used after breast cancer treatment, particularly if the tumor was hormone receptor–positive. Even pregnancy has not been associated with shortened survival of patients rendered disease free—yet many oncologists are reluctant to advise a young patient with breast cancer that it is safe to become pregnant. The use of estrogen replacement for conditions such as osteoporosis, vaginal dryness, and hot flushes may be considered for a woman with a history of breast cancer after discussion of the benefits and risks; however, it is not routinely recommended, especially given the availability of nonhormonal agents for these conditions (such as bisphosphonates and denosumab for osteoporosis).

A. Local Recurrence

The incidence of local recurrence correlates with tumor size, the presence and number of involved axillary nodes, the histologic type of tumor, the presence of skin edema or skin and fascia fixation with the primary tumor, and the type of definitive surgery and local irradiation. Local recurrence on the chest wall after total mastectomy and axillary dissection develops in as many as 8% of patients. When the axillary nodes are not involved, the local recurrence rate is less than 5%, but the rate is as high as 25% when they are heavily involved. A similar difference in local recurrence rate is noted between small and large tumors. Factors such as multifocal cancer, in situ tumors, lymphovascular invasion, positive resection margins, chemotherapy, and radiotherapy have an effect on local recurrence in patients treated with breast-conserving surgery. Adjuvant systemic therapy greatly decreases the rate of local recurrence. Genomic analysis with identification of high mutation scores also predicts local recurrence.

Chest wall recurrences usually appear within the first several years but may occur as late as 15 or more years after mastectomy. All suspicious nodules and skin lesions should be biopsied. Local excision or localized radiotherapy may be feasible if an isolated nodule is present. If lesions are multiple or accompanied by evidence of regional involvement in the internal mammary or supraclavicular nodes, the disease is best managed by radiation treatment of the entire chest wall including the parasternal, supraclavicular, and axillary areas as well as systemic therapy.

Local recurrence after mastectomy usually signals the presence of widespread disease and is an indication for tests to search for metastases. Distant metastases will develop within a few years in most patients with locally recurrent tumor after mastectomy. When there is no evidence of metastases beyond the chest wall and regional nodes, irradiation for cure after complete local excision should be attempted. After partial mastectomy, local recurrence does not have as serious a prognostic significance as after mastectomy. However, those patients in whom a recurrence develops have a worse prognosis than those who do not. It is speculated that the ability of a cancer to

recur locally after radiotherapy is a sign of aggressiveness and resistance to therapy. Completion of the mastectomy should be done for local recurrence after partial mastectomy; some of these patients will survive for prolonged periods, especially if the breast recurrence is DCIS or occurs more than 5 years after initial treatment. Systemic chemotherapy or hormonal treatment should be used for women in whom disseminated disease develops or those in whom local recurrence occurs. In rare cases, re-irradiation with accelerated partial breast techniques may be effective.

B. Breast Cancer Survivorship Issues

Given that most women with nonmetastatic breast cancer will be cured, a significant number of women face survivorship issues stemming from either the diagnosis or the treatment of the breast cancer, or both. These challenges include psychological struggles, cognitive dysfunction (also called "chemo brain"), upper extremity lymphedema, weight management problems, cardiovascular issues, bone loss, postmenopausal side effects, and fatigue. One randomized study reported that survivors who received psychological intervention from the time of diagnosis had a lower risk of recurrence and breast cancer–related mortality. A randomized study in older, overweight cancer survivors showed that diet and exercise reduced the rate of self-reported functional decline compared with no intervention.

1. Edema of the arm—Significant edema of the arm occurs in about 10–30% of patients after axillary dissection with or without mastectomy. It occurs more commonly in obese women, in women who had radiotherapy, and in women who had postoperative infection. Partial mastectomy with radiation to the axillary lymph nodes is followed by chronic edema of the arm in 10–20% of patients. Sentinel lymph node dissection has proved to be an accurate form of axillary staging without the side effects of edema or infection. Judicious use of radiotherapy, with treatment fields carefully planned to spare the axilla as much as possible, can greatly diminish the incidence of edema, which will occur in only 5% of patients if no radiotherapy is given to the axilla after a partial mastectomy and lymph node dissection.

Late or secondary edema of the arm may develop years after treatment as a result of axillary recurrence or infection in the hand or arm, with obliteration of lymphatic channels. When edema develops, a careful examination of the axilla for recurrence or infection is performed. Infection in the arm or hand on the dissected side should be treated with antibiotics, rest, and elevation. If there is no sign of recurrence or infection, the swollen extremity should be treated with rest and elevation. A mild diuretic may be helpful. If there is no improvement, a compressor pump or manual compression decreases the swelling, and the patient is then fitted with an elastic glove or sleeve. Most patients are not bothered enough by mild edema to wear an uncomfortable glove or sleeve and will treat themselves with elevation or manual compression alone. Rarely, edema may be severe enough to interfere with use of the limb. A prospective randomized study has shown that twice weekly progressive weight lifting improves lymphedema symptoms and exacerbations and improves extremity strength.

2. Breast reconstruction—Breast reconstruction is usually feasible after total or modified radical mastectomy. Reconstruction should be discussed with patients prior to mastectomy, because it offers an important psychological focal point for recovery. Reconstruction is not an obstacle to the diagnosis of recurrent cancer. The most common breast reconstruction has been implantation of a silicone gel or saline prosthesis in the subpectoral plane between the pectoralis minor and pectoralis major muscles. Alternatively, autologous tissue can be used for reconstruction.

Autologous tissue flaps have the advantage of not feeling like a foreign body to the patient. The most popular autologous technique is reconstruction using abdominal tissue flaps. This includes the deep inferior epigastric perforator (DIEP) flap and the more traditional transrectus abdominis muscle (TRAM) flap. A latissimus dorsi flap can be swung from the back but offers less volume than the TRAM flap and thus often requires supplementation with an implant. Reconstruction may be performed immediately (at the time of initial mastectomy) or may be delayed until later, usually when the patient has completed adjuvant therapy. When considering reconstructive options, concomitant illnesses should be considered, since the ability of an autologous flap to survive depends on medical comorbidities. In addition, the need for radiotherapy may affect the choice of reconstruction as radiation may increase fibrosis around an implant or decrease the volume of a flap. Skin-sparing and nipple-sparing mastectomies with immediate reconstruction, when feasible, may afford superior cosmetic outcomes.

3. Risks of pregnancy—Clinicians are often asked to advise patients regarding the potential risk of future pregnancy after definitive treatment for early-stage breast cancer. *To date, no adverse effect of pregnancy on survival of women who have had breast cancer has been demonstrated.* When counseling patients, oncologists must take into consideration the patients' overall prognosis, age, comorbidities, and life goals.

In patients with inoperable or metastatic cancer (stage IV disease), induced abortion may be advisable because of the possible adverse effects of hormonal treatment, radiotherapy, or chemotherapy upon the fetus in addition to the expectant mother's poor prognosis.

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CARCINOMA OF THE MALE BREAST

ESSENTIALS OF DIAGNOSIS

- A painless lump beneath the areola in a man usually over 50 years of age.
- Nipple discharge, retraction, or ulceration may be present.
- Generally poorer prognosis than in women.

General Considerations

Breast cancer in men is a rare disease; the incidence is only about 1% of all breast cancer diagnoses. The average age at occurrence is about 70 years, and there may be an increased incidence of breast cancer in men with prostate cancer. As in women, hormonal influences are probably related to the development of male breast cancer. There is a high incidence of both breast cancer and gynecomastia in Bantu men, theoretically owing to failure of estrogen inactivation by associated liver disease. It is important to note that first-degree relatives of men with breast cancer are considered to be at high risk. This risk should be taken into account when discussing options with the patient and family. In addition, *BRCA2* mutations are common in men with breast cancer. Men with breast cancer, especially with a history of prostate cancer, should receive genetic counseling.

Clinical Findings

A painless lump, occasionally associated with nipple discharge, retraction, erosion, or ulceration, is the primary complaint. Examination usually shows a hard, ill-defined, nontender mass beneath the nipple or areola. Gynecomastia not uncommonly precedes or accompanies breast cancer in men and may itself be a risk factor. Nipple discharge is an uncommon presentation for breast cancer in men but is an ominous finding associated with carcinoma in nearly 75% of cases.

Breast cancer staging is the same in men as in women. Gynecomastia and metastatic cancer from another site (eg, prostate) must be considered in the differential diagnosis. Benign tumors are rare, and biopsy should be performed on all males with a defined breast mass.

Treatment

Treatment consists of modified radical mastectomy in operable patients, who should be chosen by the same criteria as women with the disease. Breast-conserving therapy remains underutilized. Irradiation is the first step in treating localized metastases in the skin, lymph nodes, or skeleton that are causing symptoms. Examination of the cancer for hormone receptors and *HER2* overexpression is of value in determining adjuvant therapy. Over 95% of men have ER-positive tumors and less than 10% have overexpression of *HER2*. Androgen receptor is also commonly overexpressed in male breast cancer, though this does not impact systemic therapy decisions. Adjuvant systemic therapy and radiation are used for the same indications as in breast cancer in women.

Because breast cancer in men is frequently hormone receptor–positive, diagnosed late, and is a disseminated disease, endocrine therapy is of considerable importance in its management. Tamoxifen is the main medication for management of advanced breast cancer in men. Tamoxifen (20 mg orally daily) should be the initial treatment. There are few data regarding the use of AIs in men, but they are used frequently. Castration in advanced breast cancer is a successful measure and more beneficial than the same procedure in women but is rarely used. Objective evidence of regression may be seen in 60–70% of men with endocrine therapy for metastatic disease—approximately twice the proportion in women. Bone is the most frequent site of metastases from breast cancer in men (as in women), and endocrine therapy relieves bone pain in most patients so treated. The longer the interval between mastectomy and recurrence, the longer is the remission following treatment.

Chemotherapy should be administered for the same indications and using the same dosage schedules as for women with metastatic disease or for adjuvant treatment.

Prognosis

A large population-based, international breast cancer study reported that after adjustment for prognostic features (age, stage, treatment), men have a similar relative survival stage for stage compared to women. For node-positive disease, 5-year survival is approximately 69%, and for node-negative disease, it is about 88%.

For those patients whose disease progresses despite treatment, meticulous efforts at palliative care are essential (see Chapter 5).

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Gynecologic Disorders

Jill Brown, MD, MPH, MHS, FACOG[1]
Katerina Shvartsman, MD, FACOG[1]

18

ABNORMAL UTERINE BLEEDING IN WOMEN OF REPRODUCTIVE AGE

ESSENTIALS OF DIAGNOSIS

- Accurate diagnosis of abnormal uterine bleeding (AUB) depends on appropriate categorization and diagnostic tests.
- Evaluating AUB depends on the age and risk factors of the patient.
- Pregnancy should always be ruled out as a cause of AUB in reproductive age women.

General Considerations

Normal menstrual frequency varies from 24 to 38 days with bleeding lasting an average of 5 days (range, 2–8 days) and a mean blood loss of 40 mL per cycle. AUB refers to menstrual bleeding of abnormal quantity, duration, or schedule. The International Federation of Gynecology and Obstetrics (FIGO) introduced the classification system for AUB in 2011, which was then endorsed by the American College of Obstetrics and Gynecology. This classification system pairs AUB with descriptive terms denoting the bleeding pattern (ie, **heavy**, **light** and **menstrual**, **intermenstrual**) and etiology (the acronym **PALM-COEIN** standing for **P**olyp, **A**denomyosis, **L**eiomyoma, **M**alignancy and hyperplasia, **C**oagulopathy, **O**vulatory dysfunction, **E**ndometrial, **I**atrogenic, and **N**ot yet classified). In adolescents, AUB often occurs because of persistent **anovulation** due to the immaturity of the hypothalamic-pituitary-ovarian axis. Once regular menses have been established during adolescence, **ovulatory dysfunction** AUB (AUB-O) accounts for most cases. AUB in women aged 19–39 years is often a result of pregnancy, structural lesions, anovulatory cycles, use of hormonal contraception, or endometrial hyperplasia.

[1]Dr. Brown and Dr. Shvartsman are employees of the Uniformed Services University (USU). The opinions and assertions expressed in this chapter are Dr. Brown's and Dr. Shvartsman's and do not reflect the official policy or position of the USU or the Department of Defense.

Clinical Findings

A. Symptoms and Signs

The diagnosis depends on the following: (1) confirming uterine source of the bleeding; (2) excluding pregnancy and confirming patient is premenopausal; (3) ascertaining whether the bleeding pattern suggests regular ovulatory bleeding or anovulatory bleeding; (4) determining contribution of structural abnormalities (PALM), including risk for malignancy/hyperplasia; (5) identifying risk of medical conditions that may impact bleeding (eg, inherited bleeding disorders, endocrine disease, risk of infection); and (6) assessing contribution of medications, including contraceptives, anticoagulants, and natural product supplements that may affect bleeding.

B. Laboratory Studies

A CBC, pregnancy test, and thyroid tests should be done. For adolescents with heavy menstrual bleeding and adults with a positive screening history for bleeding disorders, coagulation studies should be considered, since up to 18% of women with severe heavy menstrual bleeding have an underlying coagulopathy. Vaginal or urine samples should be obtained for testing to rule out infectious causes. If indicated, cervical cytology should also be obtained.

C. Imaging

Transvaginal ultrasound is useful to assess for presence of fibroids, suspicion of adenomyosis, and to evaluate endometrial thickness. Sonohysterography or hysteroscopy may help to diagnose endometrial polyps or subserous myomas. MRI is not a primary imaging modality for AUB but can more definitively diagnose submucous myomas and adenomyosis.

D. Endometrial Sampling

The purpose of endometrial sampling is to determine if hyperplasia or carcinoma is present. Sampling methods

Table 18–1. Common gynecologic diagnostic procedures.

Colposcopy	Visualization of cervical, vaginal, or vulvar epithelium under 5–50 × magnification with and without dilute acetic acid to identify abnormal areas requiring biopsy. An office procedure.
Dilation & curettage (D&C)	Dilation of the cervix and curettage of the entire endometrial cavity, using a metal curette or suction cannula and often using forceps for the removal of endometrial polyps. Can usually be done in the office under local anesthesia or in the operating room under sedation or general anesthesia. D&C is often combined with hysteroscopy for improved sensitivity.
Endometrial biopsy	Blind sampling of the endometrium by means of a curette or small aspiration device without cervical dilation. Diagnostic accuracy similar to D&C. An office procedure performed with or without local anesthesia.
Endocervical curettage	Removal of endocervical epithelium with a small curette for diagnosis of cervical dysplasia and cancer. An office procedure performed with or without local anesthesia.
Hysterosalpingography	Injection of radiopaque dye through the cervix to visualize the uterine cavity and oviducts. Mainly used in investigation of infertility or to identify a space-occupying lesion.
Hysteroscopy	Visual examination of the uterine cavity with a small fiberoptic endoscope passed through the cervix. Curettage, endometrial ablation, biopsies of lesions, and excision of myomas or polyps can be performed concurrently. Can be done in the office under local anesthesia or in the operating room under sedation or general anesthesia. Greater sensitivity for diagnosis of uterine pathology than D&C.
Laparoscopy	Visualization of the abdominal and pelvic cavity through a small fiberoptic endoscope passed through a subumbilical incision. Permits diagnosis, tubal sterilization, and treatment of many conditions previously requiring laparotomy. General anesthesia is used.
Saline infusion sonohysterography	Introduction of saline solution into endometrial cavity with a catheter to visualize submucous myomas or endometrial polyps by transvaginal ultrasound. May be performed in the office with oral or local analgesia, or both.

and other gynecologic diagnostic procedures are described in Table 18–1. Polyps, endometrial hyperplasia and, occasionally, submucous myomas are identified on endometrial biopsy. Endometrial sampling should be performed in patients with AUB who are 45 years or older, or in younger patients with a history of unopposed estrogen exposure (including obesity or chronic ovulatory dysfunction) or failed medical management and persistent AUB.

Treatment

Treatment for premenopausal patients with AUB depends on the etiology of the bleeding, determined by history, physical examination, laboratory findings, imaging, and endometrial sampling. Patients with AUB due to structural abnormalities (eg, submucosal myomas, endometrial polyps, or pelvic [endometrial] neoplasms) or bleeding diathesis (thrombophilias) may require targeted therapy. A large proportion of premenopausal patients, however, have ovulatory dysfunction AUB (AUB-O).

Treatment for AUB-O should include consideration of potentially contributing medical conditions, such as thyroid dysfunction. Often AUB-O can be treated hormonally. For women amenable to using contraceptives, estrogen-progestin contraceptives and the 52-mg levonorgestrel-releasing intrauterine device (IUD) are both effective treatments. The choice between the two depends on whether any contraindications to these treatments exist and on patient preference. Oral or injectable progestin-only medications are also generally effective, but there is little consensus on optimal regimens, and they appear to be less effective than other medical therapies like the hormonal IUD and tranexamic acid. Nonhormonal options include NSAIDs, such as naproxen or mefenamic acid, in the usual anti-inflammatory doses taken during menses, and tranexamic acid 1300 mg three times per day orally for up to 5 days. Both have been shown to decrease menstrual blood loss by about 40%, with tranexamic acid superior to NSAIDs in direct comparative studies.

Women who are experiencing heavier bleeding can be given a taper of any of the combination oral contraceptives (with 30–35 mcg of ethinyl estradiol) to control the bleeding. There are several commonly used contraceptive dosing regimens, including one pill three times daily (every 8 hours) for 1 or 2 days followed by one pill twice daily through day 5 and then one pill daily through day 20; after withdrawal bleeding occurs, pills are taken in the usual dosage for three cycles. In cases of heavy bleeding requiring hospitalization, intravenous conjugated estrogens, 25 mg every 4 hours for three or four doses, can stop acute bleeding. This can be followed by oral conjugated estrogens, 2.5 mg daily, or ethinyl estradiol, 20 mcg orally daily, for 3 weeks, with the addition of medroxyprogesterone acetate, 10 mg orally daily for the last 10 days of treatment, or a combination oral contraceptive daily for 3 weeks. This will stabilize the endometrium and control the bleeding.

For women with ineffective results from medical management or who do not desire medical management, surgical options can be considered. Heavy menstrual bleeding due to structural lesions (eg, fibroids, adenomyosis, polyps) is the most common indication for surgery. Minimally invasive procedural options for fibroids include uterine artery embolization and focused ultrasound ablation. Surgical options include myomectomy or hysterectomy. For adenomyosis, the definitive treatment is hysterectomy. Polyps can often be excised hysteroscopically. For women without structural abnormalities, endometrial ablation has similar results compared to the hormonal IUD in reducing menstrual blood loss. Hysteroscopic surgical approaches include endometrial ablation with laser photocoagulation or electrocautery. Nonhysteroscopic techniques include balloon thermal ablation, cryoablation, free-fluid thermal ablation, impedance bipolar radiofrequency ablation, and microwave ablation. The latter methods are well-adapted to outpatient therapy under local anesthesia. While hysterectomy was used commonly in the past for bleeding

unresponsive to medical therapy, the low risk of complications and the good short-term results of both endometrial ablation and hormonal IUD make them attractive alternatives to hysterectomy.

When to Refer

- If bleeding is not controlled with first-line therapy.
- If expertise is needed for a surgical procedure.

When to Admit

If bleeding is uncontrollable with first-line therapy or the patient is not hemodynamically stable.

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Bofill Rodriguez M et al. Cyclical progestogens for heavy menstrual bleeding. Cochrane Database Syst Rev. 2019;8: CD001016. [PMID: 31425626]
Bryant-Smith AC et al. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev. 2018;4:CD000249. [PMID: 29656433]
Wouk N et al. Abnormal uterine bleeding in premenopausal women. Am Fam Physician. 2019;99:435. [PMID: 30932448]

POSTMENOPAUSAL UTERINE BLEEDING

ESSENTIALS OF DIAGNOSIS

- Any uterine bleeding in a postmenopausal woman (12 months or more following cessation of menstrual cycles) is abnormal and should be evaluated.
- Transvaginal ultrasound measurement of the endometrium is an important tool in evaluating the cause of postmenopausal bleeding.

General Considerations

Menopause is defined as 1 year without menstrual bleeding. The most common causes of postmenopausal bleeding are endometrial atrophy, endometrial proliferation or hyperplasia, endometrial or cervical cancer, and administration of estrogens without or with added progestin. Other causes include atrophic vaginitis, trauma, endometrial polyps, abrasion of the cervix associated with prolapse of the uterus, and blood dyscrasias.

Diagnosis

The vulva and vagina should be inspected for areas of bleeding, ulcers, or neoplasms. Cervical cytology should be obtained, if indicated. Transvaginal sonography should be used to measure endometrial thickness. An endometrial stripe measurement of 4 mm or less indicates a low likelihood of hyperplasia or endometrial cancer. If the endometrial thickness is greater than 4 mm, endometrial sampling is indicated. If there is focal thickening of the endometrium on ultrasound or persistent bleeding despite negative results on endometrial biopsy, guided sampling with hysteroscopy is more appropriate than random endometrial sampling.

Treatment

Management options for endometrial hyperplasia without atypia include surveillance, oral contraceptives, or progestin therapy. Surveillance may be used if the risk of occult cancer or progression to cancer is low and the inciting factor (eg, anovulation) has been eliminated. Therapy may include taking cyclic or continuous progestin therapy (medroxyprogesterone acetate, 10–20 mg/day orally, or norethindrone acetate, 15 mg/day orally) or using a hormonal IUD. Repeat sampling should be performed if symptoms recur. Hysterectomy is the preferred treatment for endometrial hyperplasia with atypia (also called endometrial intraepithelial neoplasia) or carcinoma of the endometrium. In some patients with endometrial hyperplasia with atypia, progestin therapy with scheduled repeat endometrial sampling may be an alternative to hysterectomy. Patients who elect this approach include those who desire future childbearing or those who are not candidates for surgery.

When to Refer

- Expertise in performing ultrasonography is required.
- Endometrial hyperplasia with atypia is present.
- Hysteroscopy is indicated.

Khafaga A et al. Abnormal uterine bleeding. Obstet Gynecol Clin North Am. 2019;46:595. [PMID: 31677744]
Saccardi C et al. Endometrial cancer risk prediction according to indication of diagnostic hysteroscopy in post-menopausal women. Diagnostics (Basel). 2020;10:257. [PMID: 32349386]

LEIOMYOMA OF THE UTERUS (Fibroid Tumor)

ESSENTIALS OF DIAGNOSIS

- Irregular enlargement of the uterus (may be asymptomatic).
- Heavy or irregular uterine bleeding.
- Pelvic pain, dysmenorrhea, and pressure.

General Considerations

Uterine leiomyomas are the most common benign neoplasm of the female genital tract. They are discrete, round, firm, often multiple, uterine tumors composed of smooth muscle and connective tissue. The most commonly used classification is by anatomic location: (1) intramural,

(2) submucous, (3) subserous, and (4) cervical. Submucous myomas may become pedunculated and descend through the cervix into the vagina.

Clinical Findings

A. Symptoms and Signs

In nonpregnant women, myomas are frequently asymptomatic. The two most common symptoms of uterine leiomyomas for which women seek treatment are AUB and pelvic pain or pressure. Occasionally, degeneration occurs, causing intense pain. Myomas that significantly distort the uterine cavity may affect pregnancy by interfering with implantation, rapidly distending in early pregnancy, or impairing uterine contractility postpartum. Torsion of subserosal pedunculated fibroids may lead to necrosis and pain.

B. Laboratory Findings

Iron deficiency anemia may result from blood loss.

C. Imaging

Ultrasonography will confirm the presence of uterine myomas and can be used sequentially to monitor growth. MRI can delineate intramural and submucous myomas accurately and is typically used before uterine artery embolization to determine fibroid size and location in relation to uterine blood supply. Hysterography or hysteroscopy can also confirm cervical or submucous myomas.

Differential Diagnosis

Irregular myomatous enlargement of the uterus must be differentiated from the similar, but symmetric enlargement that may occur with pregnancy or adenomyosis. Subserous myomas must be distinguished from ovarian tumors. Leiomyosarcoma is an unusual tumor occurring in 0.5% of women operated on for symptomatic myomas. It is rare under the age of 40 but increases in incidence thereafter.

Treatment

A. Nonsurgical Measures

Women who have small asymptomatic myomas can be managed expectantly and evaluated annually. In patients wishing to defer surgical management, nonhormonal therapies (such as NSAIDs and tranexamic acid) have been shown to decrease menstrual blood loss. Women with heavy bleeding related to fibroids may respond to estrogen-progestin oral contraceptives or the hormonal IUD, although an IUD cannot be used with a distorted cavity or cavity length greater than 10 cm. Hormonal therapies, such as GnRH agonists, GnRH antagonists, and selective progesterone receptor modulators (eg, low-dose mifepristone and ulipristal acetate), have been shown to reduce myoma volume, uterine size, and menstrual blood loss. The FDA has also approved the combination of relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg (Myfembree) as the first once-daily treatment for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women with a treatment duration of up to 24 months.

However, ulipristal acetate was withdrawn from the market in the European Union and Canada as of September 2020 due to rare reports of serious drug-induced liver injury. And selective progesterone receptor modulators are not approved for fibroid treatment in the United States.

B. Surgical Measures

Surgical intervention is based on the patient's symptoms, desire for future fertility or uterine preservation, and long-term treatment goals. A variety of surgical measures are available for the treatment of myomas: myomectomy (hysteroscopic, laparoscopic, or abdominal) and hysterectomy (vaginal, laparoscopy-assisted vaginal, laparoscopic, abdominal, or robotic). Submucous myomas may be amenable to hysteroscopic resection. Myomectomy is the surgical treatment of choice for women who wish to preserve fertility.

Because the risk of surgical complications increases with the increasing size of the myoma, preoperative reduction of myoma size is sometimes desirable before hysterectomy. GnRH analogs, such as depot leuprolide, 3.75 mg intramuscularly monthly, can be used preoperatively for 3- to 4-month periods to temporarily reduce the size of myomas and surrounding vascularity. GnRH analogs also can be a bridge to surgery in patients who are anemic. By stopping menses, patients may increase their hemoglobin level, perhaps decreasing their need for blood transfusion perioperatively.

Uterine artery embolization is a minimally invasive treatment for uterine fibroids. In uterine artery embolization, the goal is to block the blood vessels supplying the fibroids, causing them to shrink. Magnetic resonance–guided high-intensity focused ultrasound, myolysis/radiofrequency ablation, and laparoscopic or vaginal occlusion of uterine vessels are newer interventions used to treat fibroids with a smaller body of evidence to support their use.

Prognosis

In women desiring future fertility, myomectomy may be offered. Patients should be counseled that recurrence may occur by 40 months in 25% of cases, postoperative pelvic adhesions may impact fertility, and cesarean delivery may be necessary secondary to disruption of the myometrium. Approximately 80% of women have long-term improvement in symptoms following uterine artery embolization. However, direct comparison of women with symptomatic fibroids who underwent myomectomy or uterine artery embolization showed that fibroid-related quality of life at 2 years post-procedure was higher among women who underwent myomectomy. Definitive surgical therapy (ie, hysterectomy) is curative.

When to Refer

Refer to a gynecologist for treatment of symptomatic leiomyomata.

When to Admit

For acute abdomen associated with an infarcted leiomyoma or for hemorrhage not controlled by outpatient measures.

Al-Hendy A et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. N Engl J Med. 2021;384:630. [PMID: 33596357]
Ali M et al. An evaluation of relugolix/estradiol/norethindrone acetate for the treatment of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. Expert Opin Pharmacother. 2022;23:421. [PMID: 35068291]
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CERVICAL POLYPS

ESSENTIALS OF DIAGNOSIS

- Irregular or postcoital bleeding.
- Polyps visible in the cervical os on speculum examination.

Clinical Findings

Cervical polyps commonly occur during the reproductive years, particularly after age 40, and are occasionally noted in postmenopausal women. The cause is not known, but inflammation may play an etiologic role. The principal symptoms are discharge and abnormal vaginal bleeding. However, abnormal bleeding should not be ascribed to a cervical polyp without sampling the endocervix and endometrium. The polyps are visible in the cervical os on speculum examination.

Cervical polyps must be differentiated from polypoid neoplastic disease of the endometrium, small submucous pedunculated myomas, large nabothian cysts, and endometrial polyps. Cervical polyps rarely contain foci of dysplasia (0.5%) or of malignancy (0.5%). Asymptomatic polyps in women under age 45 may be left untreated.

Treatment

Cervical polyps can generally be removed in the office by avulsion with uterine packing forceps or ring forceps.

When to Refer

- Polyp with a wide base.
- Inability to differentiate endocervical from endometrial polyp.

Budak A et al. Role of endometrial sampling in cases with asymptomatic cervical polyps. J Gynecol Obstet Hum Reprod. 2019;48:207. [PMID: 30660657]

PELVIC PAIN

ESSENTIALS OF DIAGNOSIS

- Determine if pain is acute or chronic.
- Categorize if pain is cyclic or continuous.
- Consider nongynecologic causes.

1. Primary Dysmenorrhea

Primary dysmenorrhea is menstrual pain associated with menstrual cycles in the absence of pathologic findings. Primary dysmenorrhea usually begins within 1–2 years after menarche and may become progressively more severe. The frequency of cases increases up to age 20 and then decreases with both increasing age and parity. Half to three-quarters of women are affected by dysmenorrhea at some time, and 5–6% have incapacitating pain.

Clinical Findings

Primary dysmenorrhea is low, midline, wave-like, cramping pelvic pain often radiating to the back or inner thighs. Cramps may last for 1 or more days and may be associated with nausea, diarrhea, headache, and flushing. The pain is produced by uterine vasoconstriction, anoxia, and sustained contractions mediated by prostaglandins. The pelvic examination is normal between menses; examination during menses may produce discomfort, but there are no pathologic findings.

Treatment

NSAIDs (ibuprofen, ketoprofen, mefenamic acid, naproxen) and the cyclooxygenase (COX)-2 inhibitor (celecoxib) are generally helpful. The medication should be started 1–2 days before expected menses. Symptoms can be suppressed with use of combined hormonal contraceptives, depo-medroxyprogesterone acetate (DMPA), etonogestrel subdermal implant (Nexplanon), or the hormonal IUD. Oral contraceptives taken continuously can suppress menstruation completely and prevent dysmenorrhea. Other therapies that have shown some benefit include local heat, thiamine 100 mg/day orally, vitamin E 200 units/day orally, and high-frequency transcutaneous electrical nerve stimulation around the time of menses. These options may be offered to patients who desire nonhormonal therapy, although they have less supporting evidence.

2. Endometriosis

General Considerations

Endometriosis is an aberrant growth of endometrium outside of the uterus, particularly in the dependent parts of the pelvis and in the ovaries. Its principal manifestations are chronic pain and infertility. While retrograde menstruation is the most widely accepted cause, its pathogenesis and

natural course are not fully understood. The overall prevalence in the United States is 6–10%.

Clinical Findings

The clinical manifestations of endometriosis are variable and unpredictable in both presentation and course. Dysmenorrhea, chronic pelvic pain, and dyspareunia are among the well-recognized symptoms. Many women with endometriosis, however, remain asymptomatic, and most women with endometriosis have a normal pelvic examination. However, in some women, pelvic examination can disclose tender nodules in the cul-de-sac or rectovaginal septum, uterine retroversion with decreased uterine mobility, uterine tenderness, or adnexal mass or tenderness.

Endometriosis must be distinguished from pelvic inflammatory disease, ovarian neoplasms, and uterine myomas. Bowel invasion by endometrial tissue may produce blood in the stool that must be distinguished from that produced by bowel neoplasm.

Imaging is useful mainly in the presence of a pelvic or adnexal mass. Transvaginal ultrasonography is the imaging modality of choice to detect the presence of deeply penetrating endometriosis of the rectum or rectovaginal septum; MRI should be reserved for equivocal cases of rectovaginal or bladder endometriosis. A definitive diagnosis of endometriosis is made only by histology of lesions removed at surgery.

Treatment

A. Medical Treatment

Although there is no conclusive evidence that NSAIDs improve the pain associated with endometriosis, these agents are a reasonable option in appropriately selected patients. Medical treatment, using a variety of hormonal therapies, is effective in the amelioration of pain associated with endometriosis. Most of these regimens are designed to inhibit ovulation and to lower hormone levels, thus preventing cyclic stimulation of endometriotic implants and inducing atrophy. The optimum duration of hormonal therapies is not clear, and their relative merits in terms of side effects and long-term risks and benefits show insignificant differences when compared with one another and even, in mild cases, with placebo. Commonly used medical regimens include the following:

1. Combined hormonal (estrogen-progestin) contraceptives are first-line treatment because they suppress ovulation, which may inhibit stimulation of endometriosis. Any of the combination oral contraceptives, the contraceptive patch, or the vaginal ring may be used continuously, which is preferred for treatment of endometriosis. Breakthrough bleeding can be treated with conjugated estrogens, 1.25 mg orally daily for 1 week, or estradiol, 2 mg daily orally for 1 week. Alternatively, a short hormone-free interval to allow a withdrawal bleed can be used whenever bothersome breakthrough bleeding occurs.
2. Progestins, specifically oral norethindrone acetate and subcutaneous DMPA, have been approved by the US FDA for treatment of endometriosis-associated pain. The etonogestrel implant has also been shown to decrease endometriosis-related pain.
3. Intrauterine progestin, using the hormonal IUD, has been shown to be effective in reducing endometriosis-associated pelvic pain and may be considered before surgery.
4. GnRH agonists are highly effective in reducing pain associated with endometriosis; however, they are not superior to other methods such as combined hormonal contraceptives. The GnRH analog (such as long-acting injectable leuprolide acetate, 3.75 mg intramuscularly monthly, used for 6 months) suppresses ovulation. Side effects of vasomotor symptoms and bone demineralization may be relieved by "add-back" therapy, such as conjugated equine estrogen, 0.625 mg orally daily, or norethindrone, 5 mg orally daily.
5. GnRH antagonists suppress pituitary gonadotropin production and create a hypoestrogenic state, like GnRH agonists, but they are effective immediately rather than requiring 7–14 days for GnRH suppression. Injectable and oral forms (eg, cetrorelix and elagolix, respectively) are available.
6. Danazol is an androgenic medication used to treat endometriosis-associated pain. It may be used for 4–6 months in the lowest dose necessary to suppress menstruation, usually 200–400 mg orally twice daily. However, danazol has a high incidence of androgenic side effects, including decreased breast size, weight gain, acne, and hirsutism, that are more severe than with other medications available.
7. Aromatase inhibitors (such as anastrozole or letrozole) in combination with conventional therapy have been evaluated with positive results in premenopausal women with endometriosis-associated pain and pain recurrence.

B. Surgical Measures

Surgical treatment of endometriosis—particularly extensive disease—is effective both in reducing pain and in promoting fertility. Laparoscopic ablation of endometrial implants significantly reduces pain. Ablation of implants and, if necessary, removal of ovarian endometriomas enhance fertility, although subsequent pregnancy rates are inversely related to the severity of disease. Women with disabling pain for whom childbearing is not a consideration can be treated definitively with hysterectomy plus bilateral salpingo-oophorectomy. In premenopausal women, hormone replacement may then relieve vasomotor symptoms.

Prognosis

There is little systematic research regarding either the progression of the disease or the prediction of clinical outcomes. The prognosis for reproductive function in early or moderately advanced endometriosis appears to be good with conservative therapy. Hysterectomy, with bilateral salpingo-oophorectomy, often is regarded as definitive treatment of endometriosis associated with intractable pelvic pain, adnexal masses, or multiple previous ineffective conservative surgical procedures. However, symptoms may recur even after hysterectomy and oophorectomy.

When to Refer

Refer to a gynecologist for laparoscopic diagnosis or surgical treatment.

When to Admit

Rarely necessary except for acute abdomen associated with ruptured or bleeding endometrioma.

3. Other Etiologies of Pelvic Pain

Additional causes of pelvic pain may include adenomyosis, fibroids, PID, malpositioned IUD, or other abnormalities of the pelvic organs, including the bowel or bladder.

Clinical Findings

The history may be suggestive of the causes mentioned above. Physical examination may be useful to narrow the differential diagnosis.

Diagnosis

Targeted physical examination may help identify the anatomic source of pelvic pain. PID should be considered in sexually active women with pelvic pain and examination findings of cervical motion tenderness, uterine tenderness, or adnexal tenderness without another explanation for the pain. Pelvic imaging is useful for diagnosing uterine fibroids or other anomalies. Adenomyosis (the presence of endometrial glands and stroma within the myometrium) may be detected with ultrasound or MRI. Laparoscopy may help diagnose endometriosis or other pelvic abnormalities not visualized by imaging.

Treatment

Treatment should be directed at the underlying cause. For example, PID should be treated with antibiotics as described below. If pain symptoms are marked or prolonged or unresponsive to medical management, diagnostic laparoscopy may be warranted. Definitive surgery depends on the intraoperative findings and the underlying etiology. For example, adenomyosis or endometriosis may respond to hormonal approaches, but if those are unsuccessful, hysterectomy remains the definitive treatment of choice for women for whom childbearing is not a consideration.

When to Refer

- Standard therapy fails to relieve pain.
- Suspicion of pelvic pathology, such as endometriosis, leiomyomas, adenomyosis, or PID.

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PELVIC ORGAN PROLAPSE

General Considerations

Pelvic organ prolapse, including cystocele, rectocele, and enterocele, are vaginal hernias commonly seen in multiparous women. **Cystocele** is a hernia of the bladder wall into the vagina, causing a soft anterior fullness. Cystocele may be accompanied by **urethrocele,** which is not a hernia but a sagging of the urethra following its detachment from the pubic symphysis usually during childbirth. **Rectocele** is a herniation of the terminal rectum into the posterior vagina, causing a collapsible pouch-like fullness. **Enterocele** is a vaginal vault hernia containing small intestine, usually in the posterior vagina and resulting from a deepening of the pouch of Douglas. Two or all three types of hernia may occur in combination. The cause of pelvic organ prolapse is multifactorial. Risk factors include vaginal birth, genetic predisposition, advancing age, prior pelvic surgery, connective tissue disorders, and increased intra-abdominal pressure associated with obesity or straining associated with chronic constipation or coughing.

Clinical Findings

Symptoms of pelvic organ prolapse may include a sensation of a bulge or protrusion in the vagina, urinary or fecal incontinence, constipation, sense of incomplete bladder or bowel emptying, and dyspareunia.

Treatment

Treatment depends on the extent of prolapse; associated symptoms; impact on the patient's quality of life; the patient's age; and her desire to retain her uterus and ability for coitus.

A. General Measures

Supportive measures include a high-fiber diet and laxatives to improve constipation. Weight reduction in obese patients and limitation of straining and lifting are helpful. Pelvic muscle training (Kegel exercises) is a simple, noninvasive intervention that may improve pelvic function; it has demonstrated clear benefit for women with urinary or fecal symptoms, especially incontinence. Pessaries may reduce a cystocele, rectocele, or enterocele and are helpful in women who do not wish to undergo surgery or who are poor surgical candidates.

B. Surgical Measures

The most common surgical procedure is vaginal or abdominal hysterectomy with additional attention to restoring

apical support with a suspension procedure, such as vaginal uterosacral suspension, sacrospinous fixation, or by abdominal sacral colpopexy. Since stress urinary incontinence and urinary retention may coexist with apical prolapse, women should be evaluated for these conditions before surgery. An anti-incontinence procedure may be done in conjunction with prolapse surgery if indicated. Surgical mesh placed transvaginally for pelvic organ prolapse repair was introduced into clinical practice in 2002; however, in 2011 the US FDA issued warnings about concerns for serious complications associated with this practice (including mesh erosion and pain). Use of these methods subsequently declined significantly. In April 2019, the US FDA withdrew its approval of surgical mesh for the indication of transvaginal repair of pelvic organ prolapse. Patients planning to have surgical repair of pelvic organ prolapse should discuss all treatment options with their clinician. Women who have received transvaginal mesh for the surgical repair of pelvic organ prolapse and have no associated symptoms or complications should continue with their annual check-ups and other routine follow-up care. They should let their clinician know that they have a surgical mesh implant, especially if they plan to have another pelvic surgery or related medical procedure. In addition, they should notify their clinician if they develop symptoms such as persistent vaginal bleeding or discharge, pelvic or groin pain, or dyspareunia.

Generally, surgical repair of pelvic organ prolapse is reserved until after completion of childbearing. If a woman with symptomatic prolapse desires pregnancy, the same procedures for vaginal suspension can be performed without hysterectomy, though limited data on pregnancy outcomes or prolapse outcomes are available. For older women who do not desire coitus, colpocleisis, the partial obliteration of the vagina, is an effective and straightforward procedure. Uterine suspension with sacrospinous cervicocolpopexy may be an effective approach in older women who wish to avoid hysterectomy but preserve coital function.

When to Refer

- Refer to urogynecologist or gynecologist for incontinence evaluation.
- Refer if nonsurgical therapy is ineffective.
- Refer for removal of mesh if symptoms develop.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 214: pelvic organ prolapse. Obstet Gynecol. 2019;134:e126. [PMID: 31651832]

Carter P et al. Management of mesh complications following surgery for stress urinary incontinence or pelvic organ prolapse: a systematic review. BJOG. 2020;127:28. [PMID: 31541614]

Gluck O et al. Laparoscopic sacrocolpopexy: a comprehensive literature review on current practice. Eur J Obstet Gynecol Reprod Biol. 2020;245:94. [PMID: 31891897]

Hemming C et al. Surgical interventions for uterine prolapse and for vault prolapse: the two VUE RCTs. Health Technol Assess. 2020;24:1. [PMID: 32138809]

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PREMENSTRUAL SYNDROME

General Considerations

The **premenstrual syndrome (PMS)** is a recurrent, variable cluster of troublesome physical and emotional symptoms that develop during the 5 days before the onset of menses and subside within 4 days after menstruation begins. PMS intermittently affects about 40% of all premenopausal women, primarily those 25–40 years of age. In about 5–8% of affected women, the syndrome may be severe. Although not every woman experiences all the symptoms or signs at one time, many describe bloating, breast pain, headache, swelling, irritability, aggressiveness, depression, inability to concentrate, libido change, lethargy, and food cravings. When emotional or mood symptoms predominate, along with physical symptoms, and there is a clear functional impairment with work or personal relationships, the term **"premenstrual dysphoric disorder" (PMDD)** may be applied. The pathogenesis of PMS/PMDD is still uncertain, and treatment methods are mainly empiric. The clinician should provide support for both the patient's emotional and physical distress, including the following:

1. Careful evaluation of the patient, with understanding, explanation, and reassurance.
2. Advice to keep a daily diary of all symptoms for 2–3 months, such as the Daily Record of Severity of Problems, to evaluate the timing and characteristics of symptoms. If symptoms occur throughout the month rather than in the 2 weeks before menses, the patient may have depression or other mental health diagnosis instead of or in addition to PMS.

Treatment

For mild to moderate symptoms, a program of aerobic exercise; reduction of caffeine, salt, and alcohol intake; and use of alternative therapies, such as acupuncture and herbal treatments may be helpful, although these interventions remain unproven.

Medications that prevent ovulation, such as hormonal contraceptives, may lessen physical symptoms. These include continuous combined hormonal contraceptive methods (pill, patch, or vaginal ring) or GnRH agonist with "add-back" therapy (eg, conjugated equine estrogen, 0.625 mg orally daily, with medroxyprogesterone acetate, 2.5–5 mg orally daily).

When mood disorders predominate, several serotonin reuptake inhibitors have been shown to be effective in relieving tension, irritability, and dysphoria with few side effects. First-line medication therapy includes serotonergic antidepressants (citalopram, escitalopram, fluoxetine, sertraline, venlafaxine) either daily or only on symptom days. There are limited data to support the use of calcium, vitamin D, and vitamin B_6 supplementation. There is insufficient evidence to support cognitive behavioral therapy.

Yonkers KA et al. Premenstrual disorders. Am J Obstet Gynecol. 2018;218:68. [PMID: 28571724]

MENOPAUSAL SYNDROME

See Chapter 26, Endocrine Disorders.

POLYCYSTIC OVARY SYNDROME

ESSENTIALS OF DIAGNOSIS

- Clinical or biochemical evidence of hyperandrogenism.
- Oligoovulation or anovulation.
- Polycystic ovaries on ultrasonography.

General Considerations

Polycystic ovary syndrome (PCOS) is a common endocrine disorder of unknown etiology affecting 5–10% of reproductive age women. The Rotterdam Criteria, endorsed by the National Institutes of Health, identify **hyperandrogenism, ovulatory dysfunction,** and **polycystic ovaries** as the key diagnostic features of the disorder in adult women; at least two of these features must be present for diagnosis.

Clinical Findings

PCOS often presents as a menstrual disorder (ranging from amenorrhea to heavy menstrual bleeding) and infertility. Skin disorders due to peripheral androgen excess, including hirsutism and acne, are common. Patients may also show signs of insulin resistance and hyperinsulinemia, and these women are at increased risk for early-onset type 2 diabetes mellitus and metabolic syndrome. Unrecognized or untreated PCOS is a risk factor for CVD. Patients who do become pregnant are at increased risk for perinatal complications, such as gestational diabetes and preeclampsia. In addition, they have an increased long-term risk of endometrial cancer secondary to chronic exposure to unopposed estrogen.

Differential Diagnosis

Anovulation in the reproductive years may also be due to (1) premature ovarian failure (high FSH, low estradiol); (2) functional hypothalamic amenorrhea, often associated with rapid weight loss or extreme physical exertion (low to normal FSH for age); (3) discontinuation of hormonal contraceptives (return to ovulation typically occurs within 90 days); (4) pituitary adenoma with elevated prolactin (galactorrhea may or may not be present); and (5) hyperthyroidism or hypothyroidism. To rule out other etiologies in women with suspected PCOS, serum FSH, estradiol, prolactin, and TSH should be evaluated. Because of the high risk of insulin resistance and dyslipidemia, all women with suspected PCOS should have a hemoglobin A_{1C} and fasting glucose along with a lipid profile. Women with clinical evidence of androgen excess should have total testosterone, free (bioavailable) testosterone, and 17-hydroxyprogesterone measured. Women with stigmata of Cushing syndrome should have a 24-hour urinary free cortisol or a low-dose dexamethasone suppression test. Congenital adrenal hyperplasia and androgen-secreting adrenal tumors also tend to have high circulating androgen levels and anovulation with polycystic ovaries; these disorders must also be ruled out in women with presumed PCOS and high serum androgens.

Treatment

In obese patients with PCOS, weight reduction and exercise are often effective in reversing the metabolic effects and in inducing ovulation. For women who do not respond to weight loss and exercise and do not desire pregnancy, combined hormonal contraceptives are first-line treatment to manage hyperandrogenism and menstrual irregularities. Intermittent or continuous progestin therapy or a hormonal IUD may be used for endometrial protection in women who cannot or choose not to use combined hormonal contraceptives. Metformin therapy may be used as a second-line therapy to improve menstrual function. Metformin has little or no benefit in the treatment of hirsutism, acne, or infertility. Contraceptive counseling should be offered to prevent unplanned pregnancy in case of a return of ovulatory cycles. For women who are seeking pregnancy and remain anovulatory, clomiphene, letrozole, or other medications can be used for ovarian stimulation (see section on Infertility below). Women with PCOS are at greater risk than normal women for twin gestation with ovarian stimulation.

If hirsutism does not improve after 6 months of treatment with combined hormonal contraceptives, an antiandrogen, such as spironolactone, may be added. Topical eflornithine cream applied to affected facial areas twice daily for 6 months may be helpful in most women. Hirsutism may also be managed with depilatory creams, electrolysis, and laser therapy. The combination of laser therapy and topical eflornithine may be particularly effective.

Weight loss, exercise, and treatment of unresolved metabolic derangements are important in preventing CVD. Women with PCOS should be managed aggressively and should have regular monitoring of lipid profiles and glucose.

When to Refer

- If expertise in diagnosis is needed.
- If patient is infertile.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 194: polycystic ovary syndrome. Obstet Gynecol. 2018;131:e157. [PMID: 29794677]

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Huddleston HG et al. Diagnosis and treatment of polycystic ovary syndrome. JAMA. 2022;327:274. [PMID: 35040896]

Shi S et al. Letrozole and human menopausal gonadotropin for ovulation induction in clomiphene resistance polycystic ovary syndrome patients: a randomized controlled study. Medicine (Baltimore). 2020;99:e18383. [PMID: 31977842]

INFERTILITY

A couple is said to be infertile if pregnancy does not result after 1 year of normal sexual activity without contraception. Up to 20% of couples experience infertility in their reproductive lives; the incidence of infertility increases with age, with a decline in fertility beginning in the early 30s and accelerating in the late 30s. The male partner contributes to about 40% of cases of infertility, and a combination of factors is common. CDC National Survey of Family Growth data from 2011–2015 noted that 12% of women in the United States aged 15–44 report impaired fecundity.

A. Initial Testing

During the initial interview, the clinician can present an overview of infertility and discuss an evaluation and management plan. Private consultations with each partner separately are then conducted. Pertinent details (eg, sexually transmitted infection history or prior pregnancies) must be obtained. The ill effects of cigarettes, alcohol, and other recreational drugs on male fertility should be discussed. Prescription medications that impair male potency and factors that may lead to scrotal hyperthermia, such as tight underwear or frequent use of saunas or hot tubs, should be discussed. The gynecologic history should include the menstrual pattern, the use and types of contraceptives, frequency and success of coitus, and correlation of intercourse with time of ovulation. The American Society for Reproductive Medicine provides patient information on the infertility evaluation and treatment (https://www.asrm.org/topics/topics-index/infertility/).

General physical and genital examinations are performed on the female partner. Basic laboratory studies include assessment of **ovarian reserve** (eg, antimüllerian hormone, and day 3 FSH and estradiol) and thyroid function tests. If the woman has regular menses with moliminal symptoms, the likelihood of ovulatory cycles is very high. A luteal phase serum progesterone above 3 ng/mL establishes ovulation. Couples should be advised that coitus resulting in conception occurs during the 6-day window before the day of ovulation. Ovulation predictor kits have largely replaced basal body temperatures for predicting ovulation, but temperature charting may be used to identify most fertile days. Basal body temperature charts cannot predict ovulation; they can only retrospectively confirm that ovulation occurred.

A semen analysis should be completed to rule out a male factor for infertility (see Chapter 29).

B. Further Testing

1. Gross deficiencies of sperm (number, motility, or appearance) require a repeat confirmatory analysis.
2. A screening pelvic ultrasound and hysterosalpingography to identify uterine cavity or tubal anomalies should be performed. Hysterosalpingography is performed within 3 days following the menstrual period if structural abnormalities are suspected. This radiographic study will demonstrate uterine abnormalities (septa, polyps, submucous myomas) and tubal obstruction. Women who have had prior pelvic inflammatory disease or abnormal tubes seen on hysterosalpingography or laparoscopy should receive doxycycline, 100 mg orally twice daily for 5 days.
3. Absent or infrequent ovulation requires additional laboratory evaluation. Elevated FSH and low estradiol and antimüllerian hormone levels indicate ovarian insufficiency. Patients with elevated prolactin levels should be evaluated for pituitary adenoma. Women over age 35 may require further assessment of **ovarian reserve.** A markedly elevated FSH (greater than 15–20 IU/L) on day 3 of the menstrual cycle suggests inadequate ovarian reserve. Although less widely performed, a clomiphene citrate challenge test, with measurement of FSH on day 10 after administration of clomiphene from days 5–9, can help confirm a diagnosis of diminished ovarian reserve. The number of antral follicles during the early follicular phase of the cycle can provide useful information about ovarian reserve and can confirm serum testing. An antimüllerian hormone level can be measured at any time during the menstrual cycle and is less likely to be affected by hormones.
4. If all the above testing is normal, **unexplained infertility** is diagnosed. In approximately 25% of women whose basic evaluation is normal, the first-line therapy is usually controlled ovarian hyperstimulation (commonly with clomiphene citrate) and intrauterine insemination. IVF may be recommended as second-line therapy.

Treatment

A. Medical Measures

Fertility may be restored by treatment of endocrine abnormalities, particularly hypothyroidism or hyperthyroidism. Women who are anovulatory because of low body weight or exercise may become ovulatory when they gain weight or decrease their exercise levels; conversely, obese women who are anovulatory may become ovulatory with loss of even 5–10% of body weight.

B. Surgical Measures

Excision of ovarian tumors or ovarian foci of endometriosis can improve fertility. Microsurgical relief of tubal obstruction due to salpingitis or tubal ligation will reestablish fertility in many cases, although with severe disease or proximal obstruction, IVF is preferable. Peritubal adhesions or endometriotic implants often can be treated via laparoscopy.

In a male with a varicocele, sperm characteristics may be improved following surgical treatment. For men who have sperm production but obstructive azoospermia, trans-epidermal sperm aspiration or microsurgical epidermal sperm aspiration has been successful.

C. Induction of Ovulation

1. Clomiphene citrate—Clomiphene citrate stimulates gonadotropin release, especially FSH. It acts as a selective

estrogen receptor modulator, similar to tamoxifen and raloxifene, and binds to the estrogen receptor. A low level of estrogen decreases the negative feedback on the hypothalamus, thereby increasing the release of FSH and LH. When FSH and LH are present in the appropriate amounts and timing, ovulation occurs.

After a normal menstrual period or induction of withdrawal bleeding with progestin, clomiphene 50 mg orally should be given daily for 5 days, typically on days 3–7 of the cycle. If ovulation does not occur, the clomiphene dosage is increased to 100 mg orally daily for 5 days. While doses of 150 mg may be used, doses greater than 100 mg do not appear to improve clinical pregnancy rates. The rate of ovulation following clomiphene treatment is approximately 80% in the absence of other infertility factors. The pregnancy rate is 30–40%, and twinning occurs in 5% of these pregnancies. Three or more fetuses are rare (less than 0.5% of cases). Pregnancy is most likely to occur within the first three ovulatory cycles and unlikely to occur after cycle 6. In addition, several studies have suggested a twofold to threefold increased risk of ovarian cancer with the use of clomiphene for more than 1 year, so treatment with clomiphene is usually limited to a maximum of six cycles.

2. Letrozole—The aromatase inhibitor letrozole appears to be at least as effective as clomiphene for induction of ovulation in women with PCOS. There is a reduced risk of multiple pregnancy, a lack of antiestrogenic effects, and a reduced need for ultrasound monitoring. The dose of letrozole is 2.5–7.5 mg daily, starting on day 3 of the menstrual cycle. In women who have a history of estrogen-dependent tumors, such as breast cancer, letrozole is preferred over other agents because the estrogen levels with this medication are much lower.

3. Human menopausal gonadotropins (hMG) or recombinant FSH—hMG or recombinant FSH is indicated in cases of hypogonadotropism and most other types of anovulation resistant to clomiphene treatment. Because of the complexities, laboratory tests, and expense associated with this treatment, these patients should be referred to an infertility specialist.

D. Artificial Insemination in Azoospermia

If azoospermia is present, artificial insemination by a donor usually results in pregnancy, assuming female function is normal. Using frozen sperm provides the opportunity for screening for sexually transmitted infections, including HIV infection.

E. Assisted Reproductive Technology (ART)

Couples who have not responded to traditional infertility treatments and those with occlusive tubal disease, severe endometriosis, oligospermia, and immunologic or unexplained infertility, may benefit from ART. All ART procedures involve ovarian stimulation to produce multiple oocytes, oocyte retrieval by transvaginal sonography–guided needle aspiration, and handling of the oocytes outside the body. With IVF, the eggs are fertilized in vitro and the embryos transferred to the uterus. Intracytoplasmic sperm injection allows fertilization with a single sperm. While originally intended for couples with male factor infertility, it is now used in two-thirds of all IVF procedures in the United States.

The chance of a multiple gestation pregnancy (ie, twins, triplets) is increased in all assisted reproductive procedures, increasing the risk of preterm delivery and other pregnancy complications. To minimize this risk, most infertility specialists recommend transferring only one embryo in appropriately selected patients with a favorable prognosis.

Prognosis

The prognosis for conception and normal pregnancy is good if minor (even multiple) disorders can be identified and treated; it is poor if the causes of infertility are severe, untreatable, or of prolonged duration (over 3 years).

In the absence of identifiable causes of infertility, 60% of couples will achieve a spontaneous pregnancy within 3 years. Couples in which the woman is younger than 35 years who do not achieve pregnancy within 1 year of trying may be candidates for infertility treatment, and within 6 months for women age 35 years and older. Also, offering appropriately timed information about adoption is considered part of a complete infertility regimen.

When to Refer

Refer to reproductive endocrinologist if ART is indicated, or surgery is required.

American College of Obstetricians and Gynecologists. Committee Opinion No. 781: infertility workup for the women's health specialist. Obstet Gynecol. 2019;133:e377. [PMID: 31135764]

Hodgson RM et al. Interventions for endometriosis-related infertility: a systematic review and network meta-analysis. Fertil Steril. 2020;113:374. [PMID: 32106991]

Merritt BA et al. Imaging of infertility, Part 1: hysterosalpingograms to magnetic resonance imaging. Radiol Clin North Am. 2020;58:215. [PMID: 32044003]

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CONTRACEPTION & FAMILY PLANNING

Unintended pregnancies are a worldwide problem but disproportionately impact developing countries. There were 121 million unintended pregnancies annually from 2015 to 2019, corresponding to a global rate of 64 per 1000 women aged 15–49; 61% of these cases resulted in an abortion. In middle- and high-income countries, the unintended pregnancy rate fell by 21% from 1990–1994 to 2015–2019, whereas it fell by 18% in low-income countries over this time frame. It is important for primary care providers to educate their patients about the benefits of contraception and to provide options that are appropriate and desirable for the patient.

1. Oral Contraceptives

A. Combined Oral Contraceptives

1. Efficacy and methods of use—Combined oral contraceptives have a perfect use failure rate of 0.3% and a typical use failure rate of 8%. Their primary mode of action is suppression of ovulation. The pills can be started on the first day of the menstrual cycle, the first Sunday after the onset of the cycle, or on any day of the cycle. If started more than 5 days after the first day of the cycle, a backup method should be used for the first 7 days. If an active pill is missed at any time, and no intercourse occurred in the past 5 days, two pills should be taken immediately, and a backup method should be used for 7 days. If intercourse occurred in the previous 5 days, emergency contraception should be offered. A backup method should be used for 7 days.

2. Benefits of oral contraceptives—Noncontraceptive benefits of oral contraceptives include lighter menses and improvement of dysmenorrhea, decreased risk of ovarian and endometrial cancer, and improvement in acne. Functional ovarian cysts are less likely with oral contraceptive use. There is also a beneficial effect on bone mass.

3. Selection of an oral contraceptive—Any of the combination oral contraceptives containing 35 mcg or less of ethinyl estradiol or 3 mg of estradiol valerate are suitable for most women. There is some variation in potency of the various progestins in the pills, but there are essentially no clinically significant differences for most women among the progestins in the low-dose pills. There is insufficient evidence that triphasic oral contraceptives provide any benefit compared to monophasic oral contraceptives in terms of effectiveness, bleeding patterns, or discontinuation rates. Therefore, monophasic pills are recommended as a first choice for women starting oral contraceptive use. Women who have acne or hirsutism may benefit from treatment with desogestrel, drospirenone, or norgestimate, since they are the least androgenic. Pills are typically packaged in 21- or 28-day cyclic regimens but may be taken continuously to allow the user to decide if and when she has a withdrawal bleed. Studies have shown no significant risk from long-term amenorrhea in patients taking continuous oral contraceptives. The low-dose oral contraceptives commonly used in the United States are listed in Table 18–2.

4. Drug interactions—Several medications interact with oral contraceptives potentially decreasing their efficacy, typically by inducing microsomal enzymes in the liver. Some commonly prescribed medications in this category are phenytoin, phenobarbital (and other barbiturates), primidone, topiramate, carbamazepine, rifampin, and St. John's wort. Women taking these medications should use another means of contraception for maximum safety.

Antiretroviral medications, specifically ritonavir-boosted protease inhibitors, may significantly decrease the efficacy of combined oral contraceptives. Other antiretrovirals, such as nonnucleoside reverse transcriptase inhibitors, have smaller effects on oral contraceptive efficacy.

5. Contraindications and adverse effects—Oral contraceptives have been associated with many adverse effects; they are contraindicated with some conditions and should be used with caution in others (Table 18–3).

a. Myocardial infarction—The risk of MI is higher with use of oral contraceptives in certain populations, but the risk attributable to oral contraceptives is low in reproductive age women. Cigarette smoking, obesity, hypertension, diabetes mellitus, or hypercholesterolemia increases the risk. Smokers over age 35 and women with other cardiovascular risk factors should use other non-estrogen–containing methods of birth control.

b. Thromboembolic disease—A three- to fivefold increased rate of venous thromboembolism is found in oral contraceptive users, but the absolute risk is low (5–6 per 100,000 woman-years compared to a rate of 50–300 per 100,000 pregnancies). Several studies have reported a twofold increased risk in women using oral contraceptives containing the progestins, gestodene (not available in the United States), drospirenone, or desogestrel, compared with women using oral contraceptives with levonorgestrel and norethindrone. Women in whom thromboembolism develops should stop using oral contraceptives, as should those at increased risk for thromboembolism associated with surgery, fracture, serious injury, hypercoagulable condition, or immobilization. Women with a known thrombophilia should not use estrogen-containing contraceptives.

c. Cerebrovascular disease—Overall, a small increased risk of hemorrhagic stroke and subarachnoid hemorrhage and a somewhat greater increased risk of thrombotic stroke have been found; smoking, hypertension, and age over 35 years are associated with increased risk. Women should stop using estrogen-containing contraceptives if such warning symptoms as severe headache, blurred or lost vision, or other transient neurologic disorders develop.

d. Carcinoma—There is no increased risk of breast cancer in women aged 35–64 who are current or former users of oral contraceptives. Women with a family history of breast cancer or women who started oral contraceptive use at a young age are not at increased risk. Combination oral contraceptives reduce the risk of endometrial carcinoma by 40% after 2 years of use and 60% after 4 or more years of use. The risk of ovarian cancer is reduced by 30% with pill use for less than 4 years, by 60% with pill use for 5–11 years, and by 80% with use for 12 or more years. Oral contraceptives have been associated with developing benign hepatocellular adenomas and peliosis hepatis (blood-filled cavities) (but not focal nodular hyperplasia or hepatocellular carcinoma); hepatocellular adenomas may rarely cause rupture of the liver, hemorrhage, and death. The risk of hepatocellular adenoma increases with higher dosage, longer duration of use, and older age.

e. Hypertension—Oral contraceptives may cause hypertension in some women; the risk is increased with longer duration of use and older age. Women in whom hypertension develops while using oral contraceptives should use other non-estrogen–containing contraceptive methods. However, with regular blood pressure monitoring, nonsmoking women with well-controlled mild hypertension may use oral contraceptives.

Table 18–2. Commonly used low-dose oral contraceptives (listed within each group in order of increasing estrogen dose).

Name	Progestin	Estrogen (Ethinyl Estradiol)	Cost per Month[1]
Combination			
Alesse[2,3]	0.1 mg levonorgestrel	20 mcg	$35.20
Loestrin 1/20[2]	1 mg norethindrone acetate	20 mcg	$38.22
Mircette[2]	0.15 mg desogestrel	20 mcg	$59.98
Yaz[2]	3 mg drospirenone	20 mcg	$22.68
Loestrin 21 1.5/30[2]	1.5 mg norethindrone acetate	30 mcg	$34.44
Low Ogestrel[2]	0.3 mg norgestrel	30 mcg	$30.52
Levora[2]	0.15 mg levonorgestrel	30 mcg	$30.92
Desogen[2]	0.15 mg desogestrel	30 mcg	$35.55
Yasmin[2]	3 mg drospirenone	30 mcg	$22.12
Brevicon[2], Modicon[2]	0.5 mg norethindrone	35 mcg	$32.17
Demulen 1/35[2]	1 mg ethynodiol diacetate	35 mcg	$29.88
Ortho-Novum 1/35[2]	1 mg norethindrone	35 mcg	$10.33
Ortho-Cyclen[2]	0.25 mg norgestimate	35 mcg	$32.23
Gildagia[2]	0.4 mg norethindrone	35 mcg	$44.84
Combination: Extended-Cycle			
LoSeasonique (91-day cycle)[2]	0.10 mg levonorgestrel (days 1–84)/0 mg levonorgestrel (days 85–91)	20 mcg (84 days)/10 mcg (7 days)	$82.63
Amethyst (28-day pack)	90 mcg levonorgestrel	20 mcg	$59.40
Seasonique (91-day cycle)[2]	0.15 mg levonorgestrel (days 1–84)/0 mg levonorgestrel (days 85–91)	30 mcg (84 days)/10 mcg (7 days)	$67.70
Triphasic			
Estrostep[2]	1 mg norethindrone acetate (days 1–5) 1 mg norethindrone acetate (days 6–12) 1 mg norethindrone acetate (days 13–21)	20 mcg 30 mcg 35 mcg	$203.28
Cyclessa[2]	0.1 mg desogestrel (days 1–7) 0.125 mg desogestrel (days 8–14) 0.15 mg desogestrel (days 15–21)	25 mcg	$62.22
Tri-Lo-Estarylla	0.18 mg norgestimate (days 1–7) 0.215 mg norgestimate (days 8–14) 0.25 mg norgestimate (days 15–21)	25 mcg	$61.56
Trivora[2,3]	0.05 mg levonorgestrel (days 1–6) 0.075 mg levonorgestrel (days 7–11) 0.125 mg levonorgestrel (days 12–21)	30 mcg 40 mcg 30 mcg	$27.48
Ortho-Novum 7/7/7[2,3]	0.5 mg norethindrone (days 1–7) 0.75 mg norethindrone (days 8–14) 1 mg norethindrone (days 15–21)	35 mcg	$32.17
Tri Estarylla[2,3]	0.18 mg norgestimate (days 1–7) 0.215 mg norgestimate (days 8–14) 0.25 mg norgestimate (days 15–21)	35 mcg	$39.32
Tri-Norinyl[2,3]	0.5 mg norethindrone (days 1–7) 1 mg norethindrone (days 8–16) 0.5 mg norethindrone (days 17–21)	35 mcg	$73.11
Progestin-Only Pill			
Ortho Micronor[2,3]	0.35 mg norethindrone to be taken continuously	None	$36.90
Slynd	4 mg drospirenone (days 1–24)	None	$194.00

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: IBM Micromedex® Red Book (electronic version. IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www-micromedexsolutions-com.proxy.hsl.ucdenver.edu/ (cited March 27, 2022).
[2]Generic equivalent available.
[3]Multiple other brands available.

Table 18–3. Contraindications to use of combined hormonal contraceptives.

Absolute contraindications
Pregnancy
Thrombophlebitis or thromboembolic disorders (past or present)
Stroke or CAD (past or present)
Cancer of the breast (known or suspected)
Undiagnosed abnormal vaginal bleeding
Estrogen-dependent cancer (known or suspected)
Hepatocellular adenoma (past or present)
Uncontrolled hypertension
Diabetes mellitus with vascular disease
Age ≥ 35 and smoking ≥ 15 cigarettes daily
Known thrombophilia
Migraine with aura
Active hepatitis
Surgery or orthopedic injury requiring prolonged immobilization
Relative contraindications
Migraine without aura
Hypertension
Heart or kidney disease
Diabetes mellitus
Gallbladder disease
Cholestasis during pregnancy
Sickle cell disease (S/S or S/C type)
Lactation

F. Headache—Migraine or other vascular headaches may occur or worsen with pill use. If severe or frequent headaches develop while using this method, it should be discontinued. Women with migraine headaches *with aura* should not use oral contraceptives due to the increased risk of stroke.

G. Lactation—Combined oral contraceptives can impair the quantity and quality of breast milk. While it is preferable to avoid the use of combination oral contraceptives during lactation, the effects on milk quality are small and are not associated with developmental abnormalities in infants. Combination oral contraceptives should not be started earlier than 4 weeks postpartum to allow for establishment of lactation and to avoid compounding the increased risk of postpartum thromboembolic disease. Progestin-only pills, levonorgestrel implants, and DMPA are alternatives with no adverse effects on milk supply.

H. Obesity—Obese and overweight women have generally been excluded from oral contraceptive trials until recently. Obesity is an independent risk factor for thromboembolic complications. However, obese women should not be denied effective contraception because of concerns about oral contraceptive complications or efficacy. Evidence suggests that efficacy is similar for overweight and obese women as for normal-weight individuals.

I. Other disorders—Depression may occur or be worsened with oral contraceptive use. Fluid retention may occur. Patients who had cholestatic jaundice during pregnancy may develop it while taking birth control pills.

6. Minor side effects—Nausea and dizziness may occur in the first few months of pill use. Spotting or breakthrough bleeding between menstrual periods may occur; this may be helped by switching to a pill of slightly greater estrogen potency. Missed menstrual periods may occur, especially with low-dose pills. A pregnancy test should be performed if pills have been skipped or an expected menstrual period is missed. Fatigue and decreased libido can occur. Chloasma may occur, as in pregnancy, and is increased by exposure to sunlight.

B. Progestin Minipill

1. Efficacy and methods of use—A formulation containing 0.35 mg of norethindrone alone is available in the United States. The efficacy is similar to that of combined oral contraceptives but depends highly on consistent use (eg, taking the pill within the same 3-hour window every day). A progestin-only pill containing drospirenone was approved by the US FDA in 2019, and a desogestrel-only pill is available in several countries outside the United States. The minipill is believed to prevent conception by causing thickening of the cervical mucus to make it hostile to sperm, by altering ovum transport (which may account for the slightly higher rate of ectopic pregnancy with these pills), and by inhibiting implantation. Ovulation is inhibited inconsistently with this method. The minipill is begun on the first day of a menstrual cycle and then taken continuously for as long as contraception is desired; there is no "placebo week."

2. Advantages—The low dose of progestin and absence of estrogen make the minipill safe for women with contraindications to estrogen therapy. Because estrogen may decrease initial milk production during lactation, the progestin minipill is an ideal choice for breastfeeding women. It also is often tried by women who want minimal doses of hormones and by patients who are over age 35. The minipill lacks the cardiovascular side effects of combination pills.

3. Complications and contraindications—There are few contraindications to the minipill (ie, current breast cancer). The minipill typically should be avoided in women with malabsorptive disease, current or past ischemic heart disease, and history of stroke. Minipill users often have bleeding irregularities (eg, prolonged flow, spotting, or amenorrhea); such patients may need regular pregnancy tests if there is a concern about contraceptive effectiveness. Many of the absolute contraindications and relative contraindications listed in Table 18–3 apply to the minipill; however, the contraceptive benefit of the minipill may outweigh the risks for patients who smoke, who are over age 35, or who have conditions such as superficial or deep venous thrombosis or known thromboembolic disorders or diabetes mellitus with vascular disease. Minor side effects of combination oral contraceptives such as mild headache may also occur with the minipill.

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Shufelt C et al. Hormonal contraception in women with hypertension. JAMA. 2020;324:1451. [PMID: 32955577]
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2. Contraceptive Injections & Implants (Long-Acting Progestins)

The injectable progestin depot medroxyprogesterone acetate (**DMPA)** is approved for contraceptive use in the United States. There has been extensive worldwide experience with this method over the past 3 decades. The medication is given as a deep intramuscular injection of 150 mg every 3 months and has a typical use failure rate of 4%. A subcutaneous preparation, containing 104 mg of DMPA is also available in the United States. Common side effects include irregular bleeding, amenorrhea, weight gain, and headache. It is associated with bone mineral loss that is reversible after discontinuation of the method. Users commonly have irregular bleeding initially and subsequently develop amenorrhea. Ovulation may be delayed after its discontinuation. Contraindications are similar to those for the minipill.

A single-rod, subdermal progestin implant, etonogestrel (**Nexplanon**), is approved for use in the United States. Nexplanon is a 40-mm by 2-mm rod containing 68 mg of the progestin etonogestrel that is inserted in the inner aspect of the nondominant arm. It is approved for use for 3 years, but data suggest it maintains effectiveness through 5 years. Hormone levels drop rapidly after removal, and there is no delay in the return of fertility. In clinical trials, the pregnancy rate was 0.0% with 3 years of use. Typical use failure is 0.1%. The side-effect profile is similar to that of the minipill and DMPA. Irregular bleeding has been the most common reason for discontinuation.

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Horvath S et al. From uptake to access: a decade of learning from ACOG LARC program. Am J Obstet Gynecol. 2020;222:S866. [PMID: 31794720]
Teal S et al. Contraception selection, effectiveness, and adverse effects: a review. JAMA. 2021;326:2507. [PMID: 34962522]

3. Other Combined Hormonal Contraceptives

A **transdermal contraceptive patch** is available that delivers a daily dose of norelgestromin (150 mcg) and ethinyl estradiol (35 mcg) and measures 20 cm^2. The patch is applied to the lower abdomen, upper torso, or buttock once a week for 3 consecutive weeks, followed by 1 week without the patch. It appears that the average steady-state concentration of ethinyl estradiol with the patch is approximately 60% higher than with a 35-mcg pill. However, there is no evidence for an increased incidence of estrogen-related side effects. The mechanism of action, side effects, and efficacy are similar to those associated with oral contraceptives, although compliance may be better. However, discontinuation due to side effects is more frequent.

A **contraceptive vaginal ring** that releases 120 mcg of etonogestrel and 15 mcg of ethinyl estradiol daily (Nuvaring) is available. The ring is soft and flexible and is placed in the upper vagina for 3 weeks, removed, and replaced 1 week later, or can be removed and immediately replaced after 4 weeks for continuous cycling, similar to oral contraceptives. The 1-year reusable segesterone acetate/ethinyl estradiol vaginal ring (Annovera) was approved by the US FDA in 2018. The ring is worn for 3 weeks and removed for 1 week, and that pattern is repeated for a total of 13 cycles. The efficacy, mechanism of action, and systemic side effects of combined hormonal vaginal rings are similar to those associated with oral contraceptives. Ring users may experience increased vaginal discharge.

4. Intrauterine Devices

In the United States, the following IUDs are available: the hormone (levonorgestrel)-releasing **Mirena, Liletta, Kyleena,** and **Skyla** IUDs and the copper-bearing **TCu380A (Paragard).** The mechanism of action of the copper IUD is thought to involve either spermicidal or inhibitory effects on sperm capacitation and transport. The hormonal IUDs also cause thickening of cervical mucus, prevent endometrial thickening, and can inhibit ovulation. IUDs are not abortifacients.

Skyla is FDA-approved for use for 3 years, Kyleena for 5 years, Liletta for 6 years, Mirena for 7 years, and the TCu380A for 10 years. The hormonal IUDs have the advantage of reducing cramping and menstrual flow. Mirena also is FDA-approved for the treatment of heavy menstrual bleeding.

The IUD is an excellent contraceptive method for most women. The devices are highly effective, with failure rates similar to those achieved with surgical sterilization. IUDs may be used in nulliparous women and adolescents. Women who are not in mutually monogamous relationships should also use condoms for protection from sexually transmitted infections. Hormonal IUDs may have a protective effect against upper tract infection similar to that of oral contraceptives.

A. Insertion

Insertion can be performed at any time during the menstrual cycle if pregnancy can be reasonably excluded. IUDs can be safely inserted in the immediate postabortal and postpartum periods. Both types of IUDs (hormonal and copper-bearing) may be inserted up to 48 hours after vaginal delivery, or prior to closure of the uterus at the time of cesarean section. Insertion immediately following abortion

Table 18–4. Contraindications to IUD use.

Absolute contraindications
Pregnancy
Acute or subacute pelvic inflammatory disease or purulent cervicitis
Significant anatomic abnormality of uterus
Unexplained uterine bleeding
Wilson disease or copper allergy (copper IUD)
Breast cancer (hormonal IUD)
Cervical, endometrial, or gestational trophoblastic neoplasia
Relative contraindications
Active liver disease (hormonal IUD)
Menorrhagia or severe dysmenorrhea (copper IUD)

IUD, intrauterine device.

is acceptable if there is no sepsis and if follow-up insertion a month later will not be possible; otherwise, it is wise to wait until 4 weeks postabortion. NSAIDs given as premedication may be helpful.

B. Contraindications and Complications

Contraindications to use of IUDs are outlined in Table 18–4.

1. Pregnancy—The copper-containing or levonorgestrel 52-mg IUD can be inserted within 5 days following a single episode of unprotected midcycle coitus as a **postcoital contraceptive**. An IUD should not be inserted into a pregnant uterus. If pregnancy occurs as an IUD failure, there is a greater chance of spontaneous abortion if the IUD is left in situ (50%) than if it is removed (25%). Women using an IUD who become pregnant should have the IUD removed if the string is visible. It can be removed at the time of abortion if that is desired. If the string is not visible and the patient wants to continue the pregnancy, she should be informed of the increased risk of miscarriage, infection, preterm birth, and abruption. She should be informed that any flu-like symptoms such as fever, myalgia, headache, or nausea warrant immediate medical attention for possible septic abortion.

Since the risk of ectopic pregnancy is increased in IUD users who become pregnant with an IUD in situ, clinicians should search for adnexal masses in early pregnancy and should always check the products of conception for placental tissue following abortion.

2. Pelvic infection—There is an increased risk of pelvic infection during the first month following insertion; however, prophylactic antibiotics are not recommended at the time of insertion since they do not appear to decrease this risk. The subsequent risk of pelvic infection appears to be primarily related to the risk of acquiring sexually transmitted infections. Infertility rates do not appear to be increased among women who have previously used the currently available IUDs. At the time of insertion, women with an increased risk of sexually transmitted infections should be screened for gonorrhea and chlamydia. Women with a history of recent or recurrent pelvic infection are not good candidates for an IUD.

3. Heavy menstrual bleeding or severe dysmenorrhea—The copper IUD can cause heavier menstrual periods, bleeding between periods, and more cramping, so it is generally not suitable for women who already suffer from these problems. Alternatively, the hormonal IUD Mirena has been approved by the US FDA to treat heavy menstrual bleeding. NSAIDs are also helpful in decreasing bleeding and pain in IUD users.

4. Complete or partial expulsion—Spontaneous expulsion of the IUD occurs in up to 10% of women during the first year of use. Any IUD should be removed if the body of the device can be seen or felt in the cervical os.

5. Missing IUD strings—If the transcervical tail cannot be seen, this may signify unnoticed expulsion, perforation of the uterus with abdominal migration of the IUD, or simply retraction of the string into the cervical canal or uterus. Once pregnancy is ruled out, the clinician may probe for the IUD with sterile sound or forceps designed for IUD removal. If the IUD cannot be detected, pelvic ultrasound will demonstrate if the IUD is intrauterine. Alternatively, obtain anteroposterior and lateral radiographs of the pelvis to evaluate for an extrauterine IUD. If the IUD is in the abdominal cavity, it should generally be removed by laparoscopy or laparotomy. Perforations of the uterus are less likely if insertion is performed slowly, with meticulous care taken to follow directions applicable to each type of IUD.

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Turok DK et al. Levonorgestrel vs. copper intrauterine devices for emergency contraception. N Engl J Med. 2021;384:335. [PMID: 33503342]

5. Diaphragm & Cervical Cap

The **diaphragm (with contraceptive jelly)** is a safe and effective contraceptive method with features that make it acceptable to some women and not others. Typical use failure is 17%. The advantages of this method are that it has no systemic side effects and gives significant protection against pelvic infection and cervical dysplasia as well as pregnancy. The disadvantages are that it must be inserted near the time of coitus and that pressure from the rim predisposes some women to cystitis after intercourse.

The **cervical cap (with contraceptive jelly)** is similar to the diaphragm but fits snugly over the cervix only (the diaphragm stretches from behind the cervix to behind the pubic symphysis). The cervical cap is more difficult to insert and remove than the diaphragm. The main advantages are that it can be used by women who cannot be fitted for a diaphragm because of a relaxed anterior vaginal wall or by women who have discomfort with or in whom

repeated bladder infections develop with the diaphragm. However, reported typical use failure rates are 14% in nulliparous women and 29% in parous women.

Because of the small risk of toxic shock syndrome, a cervical cap or diaphragm should not be left in the vagina for over 24 hours, nor should these devices be used during the menstrual period.

6. Contraceptive Foam, Cream, Film, Sponge, Jelly, & Suppository

These products are available without prescription, are easy to use, and have typical failure rates of 10–22%. All contain the spermicide nonoxynol-9, which also has some viricidal and bactericidal activity. Nonoxynol-9 does not appear to adversely affect the vaginal colonization of hydrogen peroxide–producing lactobacilli. The US FDA requires products containing nonoxynol-9 to include a warning that the products do not protect against HIV or other sexually transmitted infections and that use of these products can irritate the vagina and rectum and may increase the risk of HIV acquisition from an infected partner. A different on-demand vaginal contraceptive, a vaginal pH regulator gel containing lactic acid–citric acid–potassium bitartrate (commercial name Phexxi), was FDA-approved for use in the United States in 2020. The supporting clinical trial estimated 27.5 pregnancies per 100 woman-years.

Phexxi—a nonhormonal contraceptive gel. Med Lett Drugs Ther. 2020;62:129. [PMID: 32970042]

7. Condom

The male condom of latex, polyurethane or animal membrane affords protection against pregnancy—equivalent to that of a diaphragm and spermicidal jelly; latex and polyurethane (but not animal membrane) condoms also offer protection against many sexually transmitted infections, including HIV. When a spermicide, such as vaginal foam, is used with the condom, perfect use failure rate is approximately 2% and typical use, 13%. The disadvantages of condoms are dulling of sensation and spillage of semen due to tearing, slipping, or leakage with detumescence of the penis. Latex condoms should not be used with oil-based lubricants since these can degrade the condom and make it less effective.

Two female condoms, one made of polyurethane and the other of synthetic nitrile, are available in the United States. The reported failure rates range from 5% to 21%; the efficacy is comparable to that of the diaphragm. These are the only female-controlled method that offers significant protection against both pregnancy and sexually transmitted infections.

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8. Contraception Based on Awareness of Fertile Periods

These methods are most effective when the couple restricts intercourse to the post-ovular phase of the cycle or uses a barrier method at other times. Well-instructed, motivated couples may achieve low pregnancy rates with fertility awareness methods. Examples of some of these include monitoring cervical mucus changes, basal body temperature fluctuations, and menstrual cycle calculations to avoid having intercourse on fertile days. However, comparative efficacy trials of these methods against other contraceptive methods do not exist.

9. Emergency Contraception

Emergency contraception can decrease the risk of pregnancy after intercourse but before the establishment of pregnancy. These methods should be started as soon as possible and within 120 hours after unprotected coitus: (1) Levonorgestrel, 1.5 mg orally as a single dose (available in the United States prepackaged as Plan B and available over-the-counter for women aged 17 years and older), has a 1–2% failure rate when taken within 72 hours. It remains efficacious up to 120 hours after intercourse, though less so compared with earlier use. (2) If the levonorgestrel regimen is not available, a combination oral contraceptive containing ethinyl estradiol and levonorgestrel 1.5 mg given twice in 12 hours may be used. Used within 72 hours, the failure rate of these regimens is approximately 3%, but antinausea medication is often necessary. (3) Ulipristal acetate, a selective progesterone receptor modulator, taken orally as a single 30 mg dose, has been shown to be more effective than levonorgestrel, especially when used between 72 and 120 hours, particularly among overweight and obese women. Patients should wait 5 days after taking ulipristal to start or restart a hormonal contraceptive method. (4) Copper or levonorgestrel 52-mg IUD insertion within 5 days after one episode of unprotected midcycle coitus will also prevent pregnancy. Copper IUD use for emergency contraception is the most effective available method, with first cycle pregnancy rates of 0.1%. All victims of sexual violence should be offered emergency contraception.

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10. Sterilization

In the United States, sterilization is the most popular method of birth control for couples who want no more children. Although sterilization is reversible in some instances, reversal surgery for both women and men is costly, complicated, and not always successful. Therefore, patients should be counseled carefully before sterilization and should view the procedure as permanent.

Female sterilization procedures include laparoscopic bipolar electrocoagulation, salpingectomy, plastic ring application on the uterine tubes, or minilaparotomy with tubal resection. Salpingectomy may be preferred for the added benefit of decreasing ovarian cancer risk. The advantages of laparoscopy are minimal postoperative

pain, small incisions, and rapid recovery. The advantages of minilaparotomy are that it can be performed with standard surgical instruments under local or general anesthesia. However, there is more postoperative pain and a longer recovery period. The cumulative 10-year failure rate for all methods combined is 1.85%, varying from 0.75% for postpartum partial salpingectomy and laparoscopic unipolar coagulation to 3.65% for spring clips; this fact should be discussed with women preoperatively. Some studies have found an increased risk of menstrual irregularities as a long-term complication of tubal ligation, but findings in different studies have been inconsistent. A method of transcervical sterilization, Essure, involving placement of an expanding nickel-titanium microcoil into the proximal uterine tube under hysteroscopic guidance, was approved by the US FDA in 2002. However, as of 2018, Essure was no longer marketed due to concerns related to complications and side effects reported by users.

Male sterilization by vasectomy is a safe, simple procedure in which the vas deferens is severed and sealed through a scrotal incision under local anesthesia. Long-term follow-up studies on vasectomized men show no excess risk of CVD. Despite past controversy, there is no definite association of vasectomy with prostate cancer.

When to Refer

Refer to experienced clinicians for etonogestrel subdermal (Nexplanon) insertion, IUD insertion, tubal occlusion or ligation, or vasectomy.

ACOG Practice Bulletin No. 208 Summary: benefits and risks of sterilization. Obstet Gynecol. 2019;133:592. [PMID: 30801465]
Mercier RJ et al. Expedited scheduling of interval tubal ligation: a randomized controlled trial. Obstet Gynecol. 2019;134:1178. [PMID: 31764727]
Zamorano AS et al. Postpartum salpingectomy: a procedure whose time has come. Am J Obstet Gynecol. 2019;220:8. [PMID: 30591122]

11. Abortion

Since the legalization of abortion in the United States in 1973, the related maternal mortality rate has fallen markedly because illegal and self-induced abortions have been replaced by safer procedures. Abortions in the first trimester of pregnancy are performed by vacuum aspiration under local anesthesia or with medical regimens. Dilation and evacuation, a variation of vacuum aspiration is generally used in the second trimester. Techniques utilizing intra-amniotic instillation of hypertonic saline solution or various prostaglandins regimens, along with medical or osmotic dilators are occasionally used after 18 weeks. Several medical abortion regimens using mifepristone and multiple doses of misoprostol have been reported as being effective in the second trimester. Overall, legal abortion in the United States has a mortality rate of less than 1:100,000. Rates of morbidity and mortality rise with length of gestation. In the United States, more than 60% of abortions are performed before 9 weeks, and more than 90% are performed before 13 weeks' gestation; only 1.2% are performed after 20 weeks. If abortion is chosen, every effort should be made to encourage the patient to seek an early procedure. In the United States, while numerous state laws limiting access to abortion and a federal law banning a rarely used variation of dilation and evacuation have been enacted, abortion remains legal and available until fetal viability (definition varies by state), under *Roe v. Wade*.

Complications resulting from abortion include retained products of conception (often associated with infection and heavy bleeding), uterine perforation, and unrecognized ectopic pregnancy. Immediate analysis of the removed tissue for placenta can exclude or corroborate the diagnosis of ectopic pregnancy. Women who have fever, bleeding, or abdominal pain after abortion should be examined; use of broad-spectrum antibiotics and reaspiration of the uterus are frequently necessary. Hospitalization is advisable if postabortal endometritis requires administration of intravenous antibiotics. Complications following illegal abortion often need emergency care for hemorrhage, septic shock, or uterine perforation.

Prophylactic antibiotics are recommended before surgical abortion; for example, a single dose of doxycycline 200 mg orally can be given 1 hour before the procedure. Rh immune globulin should be given to all Rh-negative women following abortion. Contraception should be thoroughly discussed, and contraception provided at the time of abortion. There is growing evidence to support the safety and efficacy of immediate postabortal insertion of IUDs.

Mifepristone (RU 486) is approved by the US FDA as an oral abortifacient at a dose of 200 mg orally on day 1, followed by misoprostol 800 mcg buccally 24–48 hours later. The WHO recommended regimen includes mifepristone orally followed by misoprostol vaginally, sublingually, or buccally. These combinations are 93% successful in terminating pregnancies of up to 70 days' gestation with few complications. There is a 5–10% risk of incomplete abortion requiring curettage and approximately 1% risk of requiring intervention for excessive bleeding. Overall, the risk of uterine infection is lower with medical than with surgical abortion.

Baiju N et al. Effectiveness, safety and acceptability of self-assessment of the outcome of first-trimester medical abortion: a systematic review and meta-analysis. BJOG. 2019;126:1536. [PMID: 31471989]
Mark KS et al. Risk of complication during surgical abortion in obese women. Am J Obstet Gynecol. 2018;218:238. [PMID: 29074080]
Schmidt-Hansen M et al. Follow-up strategies to confirm the success of medical abortion of pregnancies up to 10 weeks' gestation: a systematic review with meta-analyses. Am J Obstet Gynecol. 2020;222:551. [PMID: 31715147]

FEMALE SEXUAL DYSFUNCTION

General Considerations

Female sexual dysfunction is a common problem. Depending on the questions asked, surveys have shown that from 35% to 98% of women report sexual concerns. Questions

related to sexual functioning should be asked as part of the routine medical history. Three helpful questions to broach the topic are "Are you currently involved in a sexual relationship?," "With men, women, or both?," and "Do you have any sexual concerns or any pain with sex?" If the woman is not involved in a sexual relationship, she should be asked if there are any concerns that are contributing to a lack of sexual behavior. If a history of sexual dysfunction is elicited, a complete history of factors that may affect sexual function should be taken. These factors include her reproductive history (including pregnancies and mode of delivery) as well as history of infertility, sexually transmitted infection, rape or sexual violence, gynecologic or urologic disorders, endocrine abnormalities (such as diabetes mellitus or thyroid disease), neurologic problems, CVD, psychiatric disease, and current prescription and over-the-counter medication use. A detailed history of the specific sexual dysfunction should be elicited, and a gynecologic examination should focus on findings that may contribute to sexual complaints.

Etiology

A. Disorders of Sexual Desire

Sexual desire in women is a complex and poorly understood phenomenon. Emotion is a key factor. Relationship conflict, fear or anxiety related to previous sexual encounters, or history of sexual abuse or violence may contribute to a lack of desire. Physical factors such as chronic illness, fatigue, depression, and specific medical disorders (such as diabetes mellitus, thyroid disease, or adrenal insufficiency) may also contribute. Menopause and attitudes toward aging may play a role. In addition, sexual desire may be influenced by other sexual dysfunction, such as arousal disorders, dyspareunia, or anorgasmia.

B. Sexual Arousal Disorders

Sexual arousal disorders may be both subjective and objective. Sexual stimulation normally leads to genital vasocongestion and lubrication. Some women may have a physiologic response to sexual stimuli but may not subjectively feel aroused because of factors such as distractions; negative expectations; anxiety; fatigue; depression; or medications, such as SSRIs or oral contraceptives. Other women with vaginal atrophy may lack both a subjective and physiologic response to sexual stimuli.

C. Orgasmic Disorders

Despite subjective and physiologic arousal, women may experience a marked delay in orgasm, diminished sensation of an orgasm, or anorgasmia. The etiology of orgasmic disorders is complex and typically multifactorial, but the cause of a particular patient's orgasmic disorder is usually amenable to treatment.

D. Sexual Pain Disorders

Dyspareunia (female sexual pain) is defined as recurrent or persistent genital pain that is provoked by sexual contact. **Vulvodynia** is a frequent cause of dyspareunia in premenopausal women. It is defined as vulvar pain of at least 3 months' duration without an identifiable cause. The discomfort may be experienced as either constant or intermittent, focal or diffuse, and spontaneous or provoked. There are generally no physical findings, except a subset of patients may have vulvar erythema.

Vaginismus is defined as recurrent or persistent involuntary spasm of the musculature of the lower third of the vagina that interferes with sexual intercourse, resulting from fear, pain, sexual violence, or a negative attitude toward sex, and causing marked distress or interpersonal difficulty. Other medical causes of sexual pain may include vulvovaginitis; vulvar disease, including lichen planus, lichen sclerosus, and lichen simplex chronicus; and pelvic disease, such as endometriosis or chronic PID; or vaginal atrophy.

Treatment

A. Disorders of Sexual Desire

In the absence of specific medical disorders, arousal or orgasmic disorders or dyspareunia, the focus of therapy is psychological. Cognitive behavioral therapy, sexual therapy, and couples therapy may all play a role. Success with pharmacologic therapy, particularly the use of dopamine agonists or testosterone with estrogen, has been reported. For premenopausal women with hypoactive sexual desire, bremelanotide 1.75 mg subcutaneously given at least 45 minutes before sexual activity can be effective therapy.

B. Sexual Arousal Disorders

As with disorders of sexual desire, arousal disorders may respond to psychological therapy. The phosphodiesterase inhibitors used in men do not appear to benefit most women with sexual arousal disorders. However, there is evidence to suggest a role for sildenafil in women with sexual dysfunction due to multiple sclerosis, type 1 diabetes mellitus, and spinal cord injury, and a role for antidepressant medications if other approaches fail.

Flibanserin (Addyi), an antidepressant, was approved by the US FDA in August 2015 as an effective treatment of hypoactive sexual desire disorder in premenopausal women; however, to be effective, it must be used long term and it has significant risks that require specific certifications of providers and pharmacies for dispensation to patients in the United States. While this medication remains available, it is rarely prescribed.

C. Orgasmic Disorders

For many women, counseling or sex therapy may be adequate treatment. There is an FDA-cleared vacuum device that increases clitoral blood flow; it may improve the likelihood of orgasm.

D. Sexual Pain Disorders

Specific painful disorders, such as endometriosis, vulvovaginitis, vulvar dermatoses, or vaginal atrophy, should be treated as outlined in other sections of this chapter.

Vaginismus may be treated initially with sexual counseling, education about anatomy and sexual function, and

pelvic floor physical therapy by a specialized provider. The patient can be instructed in self-dilation, using a lubricated finger or dilators of graduated sizes. Before coitus (with adequate lubrication) is attempted, the patient—and then her partner—should be able to easily and painlessly introduce two fingers into the vagina. Penetration should never be forced, and the woman should always be the one to control the depth of insertion during dilation or intercourse. Injection of botulinum toxin has been used successfully in refractory cases.

Since the cause of vulvodynia is unknown, management is difficult. Few treatment approaches have been subjected to methodologically rigorous trials. A variety of topical agents have been tried, although only topical anesthetics (eg, estrogen cream and a compounded mixture of topical amitriptyline 2% and baclofen 2% in a water washable base) have been useful in relieving vulvodynia. Useful oral medications include amitriptyline in gradually increasing doses from 10 mg/day to 75–100 mg/day; gabapentin, starting at 300 mg three times daily and increasing to 1200 mg three times daily; and various SSRIs. Biofeedback and physical therapy, with a therapist experienced with the treatment of vulvar pain, have been shown to be helpful. Surgery—usually consisting of vestibulectomy—has been useful for women with introital dyspareunia. See also Chapter e6.

When to Refer

- When symptoms or concerns persist despite first-line therapy.
- For expertise in surgical procedures.

Clayton AH et al. Female sexual dysfunction. Med Clin North Am. 2019;103:681. [PMID: 31078200]
Kingsberg SA et al. Bremelanotide for the treatment of hypoactive sexual desire disorder: two randomized phase 3 trials. Obstet Gynecol. 2019;134:899. [PMID: 31599840]
Rogers RG et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for the assessment of sexual health of women with pelvic floor dysfunction. Int Urogynecol J. 2018;29:647. [PMID: 29577166]

SEXUAL VIOLENCE

ESSENTIALS OF DIAGNOSIS

- The legal definition of rape varies by state and geographic location. The term "sexual violence" is used by the CDC and will be used in this discussion. It can be committed by a stranger, but more commonly the assailant is known to the victim, including a current or former partner or spouse (a form of intimate partner violence [IPV]).
- All victims of sexual violence should be offered emergency contraception.
- The many individuals affected, the enormous health care costs, and the need for a multidisciplinary approach make sexual violence and IPV important health care issues.
- Knowledge of state laws and collection of evidence requirements are essential for clinicians evaluating possible victims of sexual violence, including IPV.

General Considerations

Rape, or sexual assault, is legally defined in different ways in various jurisdictions. Clinicians and emergency department personnel who deal with victims of sexual violence should be familiar with the laws pertaining to sexual assault in their own state. From a medical and psychological viewpoint, it is essential that persons treating victims of sexual violence recognize the nonconsensual and violent nature of the crime. About 95% of people who report sexual violence are women. Each year in the United States, 4.8 million incidents of physical or sexual assault are reported by women. Penetration may be vaginal, anal, or oral and may be by the penis, hand, or a foreign object. The assailant may be unknown to the victim or, more frequently, may be an acquaintance or even the spouse.

"Unlawful sexual intercourse," or statutory rape, is intercourse with a female before the age of majority even with her consent.

Health care providers can have a significant impact in increasing the reporting of sexual violence and in identifying resources for the victims. The International Rescue Committee has developed a multimedia training tool to encourage competent, compassionate, and confidential clinical care for sexual violence survivors in low-resource settings. They have studied this intervention in over 100 health care providers and found that knowledge increased from 49% to 62% ($P < 0.001$) and confidence from 58% to 73% ($P < 0.001$) in clinical care for sexual violence survivors following training. There was also a documented increase in eligible survivors receiving emergency contraception from 50% to 82% ($P < 0.01$), HIV postexposure prophylaxis from 42% to 92% ($P < 0.001$), and sexually transmitted infection prophylaxis and treatment from 45% to 96% ($P < 0.01$). This training encourages providers to offer care in the areas of pregnancy and sexually transmitted infection prevention as well as assistance for psychological trauma.

Because sexual violence is a personal crisis, each patient will react differently, but anxiety disorders and PTSD are common sequelae. The **rape trauma syndrome** comprises two principal phases: (1) Immediate or acute: shaking, sobbing, and restless activity may last from a few days to a few weeks. The patient may experience anger, guilt, or shame or may repress these emotions. Reactions vary depending on the victim's personality and the circumstances of the attack. (2) Late or chronic: problems related to the attack may develop weeks or months later. Sexual violence survivors are at increased risk for developing several psychological and behavioral adverse effects, including PTSD, sleep disturbances, anxiety, depression, suicide attempt, and medication misuse.

Clinicians and emergency department personnel who deal with victims of sexual violence should work with community rape crisis centers or other sources of ongoing psychological support and counseling.

Examination

The clinician who first sees the alleged victim of sexual violence should be empathetic and prepared with appropriate evidence collection and treatment materials. Standardized information and training, such as the program created by the International Rescue Committee, can be a helpful resource to the providers caring for these patients. Many emergency departments have a protocol for sexual violence victims and personnel who are trained in interviewing and examining victims of sexual violence.

Treatment

1. Give analgesics or sedatives if indicated. Administer tetanus toxoid if deep lacerations contain soil or dirt particles.
2. Give ceftriaxone, 250 mg intramuscularly, plus azithromycin, 1 g orally, to prevent gonorrhea and chlamydia. In addition, give metronidazole, 2 g orally, as a single dose to treat trichomoniasis. Incubating syphilis will probably be prevented by these medications, but the VDRL test should be repeated 6 weeks after the assault.
3. Prevent pregnancy by using one of the methods discussed under Emergency Contraception.
4. Vaccinate against hepatitis B.
5. Offer HIV prophylaxis (see Chapter 31).
6. Because women who are sexually assaulted are at increased risk for long-term psychological sequelae, such as PTSD and anxiety disorders, it is critical that the patient and her family and friends have a source of ongoing counseling and psychological support.

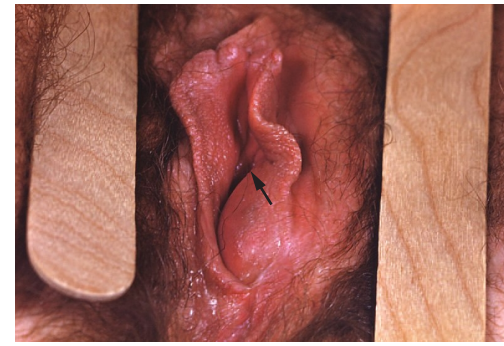
When to Refer

All women who seek care for sexual assault should be referred to a facility that has expertise in the management of victims of sexual violence and is qualified to perform expert forensic examination, if requested.

Adams JA et al. Interpretation of medical findings in suspected child sexual abuse: an update for 2018. J Pediatr Adolesc Gynecol. 2018;31:225. [PMID: 29294380]
American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 777: sexual assault. Obstet Gynecol. 2019;133:e296. [PMID: 30913202]
Pastor-Moreno G et al. Intimate partner violence during pregnancy and risk of fetal and neonatal death: a meta-analysis with socioeconomic context indicators. Am J Obstet Gynecol. 2020;222:123. [PMID: 31394067]

BARTHOLIN DUCT CYSTS & ABSCESSES

Trauma or infection may involve the Bartholin duct, causing obstruction of the gland. Drainage of secretions is obstructed, leading to pain, swelling, and abscess formation (Figure 18–1).



▲ **Figure 18–1.** Bartholin cyst (abscess). The Bartholin gland is located in the lower two-thirds of the introitus. (From Susan Lindsley, Public Health Image Library, CDC.)

The principal symptoms are periodic painful swelling on either side of the introitus and dyspareunia. A fluctuant swelling, usually 1–4 cm in diameter lateral to either labium minus, is a sign of occlusion of a Bartholin duct. Tenderness is suggestive of active infection.

Purulent drainage or secretions from the gland should be tested for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and other pathogens, and treated accordingly (see Chapter 33); frequent warm sitz baths may be helpful. Abscesses or cysts that are symptomatic should undergo incision and drainage with additional efforts to keep the drainage tract open (eg, Word catheter or marsupialization). Marsupialization should be considered for recurrence. Antibiotics are unnecessary unless cellulitis is present. In women under 40, asymptomatic cysts do not require therapy; in women over age 40, biopsy or removal should be considered to rule out vulvar carcinoma.

When to Refer

When surgical therapy (marsupialization) is indicated.

Dole DM et al. Management of Bartholin duct cysts and gland abscesses. J Midwifery Womens Health. 2019;64:337. [PMID: 30734519]
Omole F et al. Bartholin duct cyst and gland abscess: office management. Am Fam Physician. 2019;99:760. [PMID: 31194482]

VAGINITIS

ESSENTIALS OF DIAGNOSIS

- Vaginal irritation.
- Pruritus.
- Abnormal or malodorous discharge.

General Considerations

Inflammation and infection of the vagina are common gynecologic complaints, resulting from a variety of

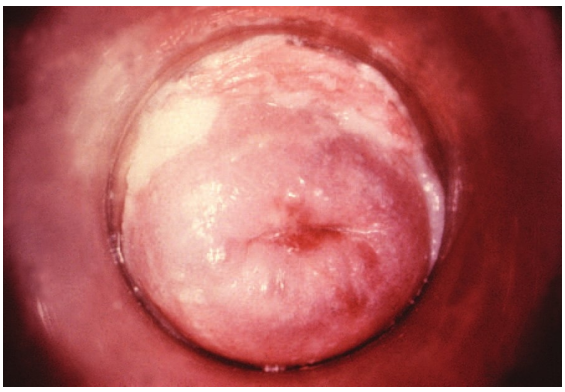
pathogens, allergic reactions to vaginal contraceptives or other products, vaginal atrophy, or friction during coitus. The normal vaginal pH is 4.5 or less, and *Lactobacillus* is the predominant organism. Normal secretions during the middle of the cycle, or during pregnancy, can be confused with vaginitis.

Clinical Findings

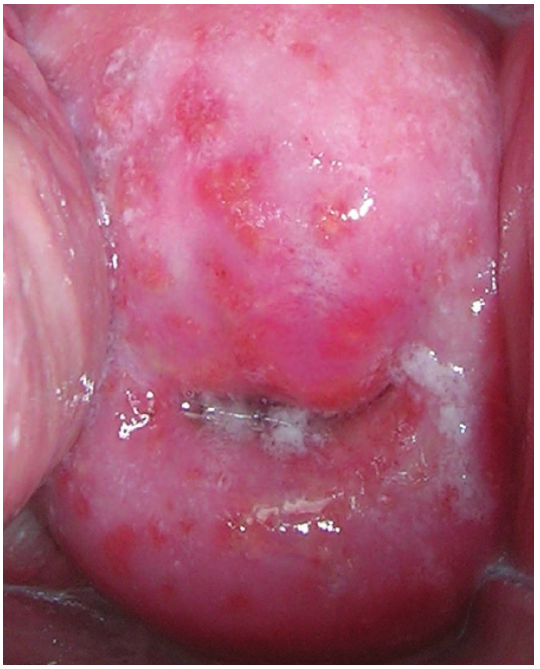
When the patient complains of vaginal irritation, pain, pruritus or unusual or malodorous discharge, a history should be taken, noting the onset, location, duration, and characterization of symptoms including triggers and alleviating factors. Additional history should include the LMP; recent sexual activity; use of contraceptives, tampons, or douches; and recent changes in medications or use of antibiotics. The physical examination should include careful inspection of the vulva and speculum examination of the vagina and cervix. A vaginal, cervical, or urine sample can be obtained for detection of gonococcus and chlamydia, if clinically indicated. Evaluation for yeast, bacterial vaginosis, and trichomonas should be performed. The vaginal pH should be tested; it is frequently greater than 4.5 in infections due to trichomonads and bacterial vaginosis. A bimanual examination to look for evidence of pelvic infection, namely cervical motion, uterine, or adnexal tenderness, should follow. Point-of-care testing is available for all three main organisms that cause vaginitis and can be used if microscopy is not available or for confirmatory testing of microscopy.

A. Vulvovaginal Candidiasis

Pregnancy, diabetes mellitus, and use of broad-spectrum antibiotics or corticosteroids predispose patients to *Candida* infections. Heat, moisture, and occlusive clothing also contribute to the risk. Pruritus, vulvovaginal erythema, and a white curd-like discharge that is not malodorous are found (Figure 18–2). Microscopic examination with 10% potassium hydroxide reveals hyphae and spores. A swab for cultures or for PCR testing may be performed if *Candida* is suspected but not demonstrated.



▲ **Figure 18–2. Cervical candidiasis.** (Public Health Image Library, CDC.)



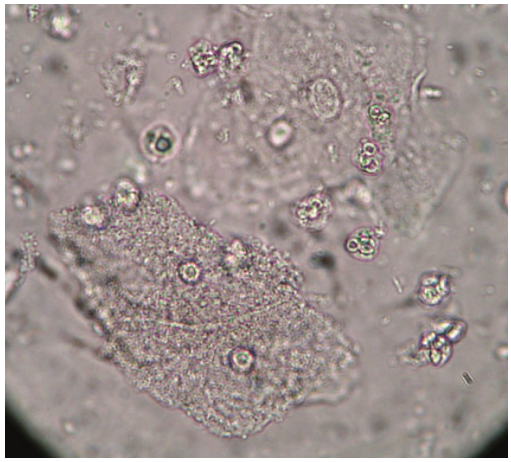
▲ **Figure 18–3. Strawberry cervix in *Trichomonas vaginalis* infection, with inflammation and punctate hemorrhages.** (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H, Tysinger J. *The Color Atlas of Family Medicine*. McGraw-Hill, 2009.)

B. *Trichomonas vaginalis* Vaginitis

This sexually transmitted protozoal flagellate infects the vagina, Skene ducts, and lower urinary tract in women and the lower genitourinary tract in men. Pruritus and a malodorous frothy, yellow-green discharge occur, along with diffuse vaginal erythema and red macular lesions on the cervix in severe cases ("**strawberry cervix**," Figure 18–3). Motile organisms with flagella seen by microscopic examination of a wet mount with saline solution is confirmatory but are identified in only 60–70% of cases. Nucleic acid amplification tests are highly sensitive and specific to identify *T vaginalis*. Other rapid diagnostic tests with improved sensitivity compared to wet mount (eg, Affirm VP III and OSOM *Trichomonas* Rapid Test) are commercially available.

C. Bacterial Vaginosis

Bacterial vaginosis is a polymicrobial disease that is *not* considered a sexually transmitted infection, but sexual activity is a risk factor. An overgrowth of *Gardnerella* and other anaerobes is often associated with increased malodorous discharge without obvious vulvitis or vaginitis. The discharge is grayish and sometimes frothy, with a pH of 5.0–5.5. An amine-like ("fishy") odor is present if a drop of discharge is alkalinized with 10% potassium hydroxide. On wet mount in saline, epithelial cells are covered with bacteria to such an extent that cell borders are obscured



▲ **Figure 18–4.** Clue cells seen in bacterial vaginosis due to *Gardnerella vaginalis.* (Reproduced with permission from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H, Tysinger J. *The Color Atlas of Family Medicine*. McGraw-Hill, 2009.)

(**clue cells**, Figure 18–4). Vaginal cultures are generally not useful in diagnosis; however, molecular testing is available.

Treatment

A. Vulvovaginal Candidiasis

A variety of topical and oral regimens are available to treat vulvovaginal candidiasis. Women with uncomplicated vulvovaginal candidiasis will usually respond to a 1- to 3-day regimen of a topical azole or a one-time dose of oral fluconazole 150 mg. Women with complicated infection (including four or more episodes in 1 year [*recurrent* vulvovaginal candidiasis], severe symptoms and signs, non-albicans species, uncontrolled diabetes mellitus, HIV infection, corticosteroid treatment, or pregnancy) should receive 7–14 days of a topical regimen or two doses of oral fluconazole 3 days apart. In recurrent non-albicans infections, boric acid 600 mg in a gelatin capsule intravaginally once daily for 2 weeks is approximately 70% effective. If recurrence occurs, referral to a gynecologist or an infectious disease specialist is indicated.

1. Single-dose regimens—Effective single-dose regimens include miconazole (1200-mg vaginal suppository), tioconazole (6.5% cream, 5 g vaginally), sustained-release butoconazole (2% cream, 5 g vaginally), or fluconazole (150-mg oral tablet).

2. Three-day regimens—Effective 3-day regimens include butoconazole (2% cream, 5 g vaginally once daily), clotrimazole (2% cream, 5 g vaginally once daily), terconazole (0.8% cream, 5 g, or 80-mg vaginal suppository once daily), or miconazole (200-mg vaginal suppository once daily).

3. Seven-day regimens—The following regimens are given once daily: clotrimazole (1% cream), miconazole (2% cream, 5 g, or 100-mg vaginal suppository), or terconazole (0.4% cream, 5 g).

4. Recurrent vulvovaginal candidiasis (maintenance therapy)—Clotrimazole (500-mg vaginal suppository once weekly or 200 mg cream twice weekly) or fluconazole (100, 150, or 200 mg orally once weekly) is an effective regimen for maintenance therapy for up to 6 months.

B. *Trichomonas vaginalis* Vaginitis

Treatment of both partners simultaneously is recommended; metronidazole 500 mg orally twice a day for 7 days or tinidazole, 2 g orally as a single dose is usually used.

In the case of treatment failure with metronidazole in the absence of reexposure, the patient should be re-treated with metronidazole or tinidazole, 2 g orally once daily for 7 days. If this is not effective in eradicating the organisms, metronidazole and tinidazole susceptibility testing can be arranged with the CDC at 404-718-4141 or at https://www.cdc.gov/std. Women infected with *T vaginalis* are at increased risk for concurrent infection with other sexually transmitted diseases (STDs) and should be offered comprehensive STD testing.

C. Bacterial Vaginosis

The recommended regimens are metronidazole (500 mg orally, twice daily for 7 days), clindamycin vaginal cream (2%, 5 g, once daily for 7 days), or metronidazole gel (0.75%, 5 g, twice daily for 5 days). Alternative regimens include clindamycin (300 mg orally twice daily for 7 days), clindamycin ovules (100 g intravaginally at bedtime for 3 days), tinidazole (2 g orally once daily for 2 days), tinidazole (1 g orally once daily for 5 days) or secnidazole (2 g oral granules in single dose). The National STD Curriculum offers a helpful training module to clinicians to review current recommendations for treatment of vaginitis (https://www.std.uw.edu/custom/self-study/vaginitis).

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 215: vaginitis in nonpregnant patient. Obstet Gynecol. 2020;135:e1. [PMID: 31856123]
Giovanini AF et al. Bacterial vaginosis and desquamative inflammatory vaginitis. N Engl J Med. 2019;380:1088. [PMID: 30865815]
Neal CM et al. Noncandidal vaginitis: a comprehensive approach to diagnosis and management. Am J Obstet Gynecol. 2020; 222:114. [PMID: 31513780]

PELVIC INFLAMMATORY DISEASE (Salpingitis, Endometritis)

ESSENTIALS OF DIAGNOSIS

- Lower abdominal or pelvic pain.
- Uterine, adnexal, or cervical motion tenderness.
- Absence of a competing diagnosis.

General Considerations

Pelvic inflammatory disease is a polymicrobial infection of the upper genital tract associated with the sexually

transmitted organisms *N gonorrhoeae* and *C trachomatis* as well as endogenous organisms, including anaerobes, *Haemophilus influenzae*, enteric gram-negative rods, and streptococci. It is most common in young, nulliparous, sexually active women with multiple partners and is a leading cause of infertility and ectopic pregnancy. The use of barrier methods of contraception may provide significant protection.

Clinical Findings

A. Symptoms and Signs

Patients with PID most commonly present with lower abdominal pain. Additional complaints may include AUB and abnormal vaginal discharge. Systemic features such as fever typically indicate more severe disease, including pelvic abscess. Right upper quadrant pain may indicate an associated perihepatitis **(Fitz-Hugh-Curtis syndrome).** Diagnosis of PID is complicated by the fact that women may have subtle or mild symptoms that are not readily recognized as PID, such as postcoital bleeding, urinary frequency, or low back pain.

B. Minimum Diagnostic Criteria

PID is diagnosed clinically. Women with cervical motion, uterine, or adnexal tenderness meet diagnostic criteria for PID and should be treated with antibiotics unless there is a competing diagnosis, such as ectopic pregnancy or appendicitis.

C. Additional Criteria

No single historical, physical, or laboratory finding is definitive for acute PID. The following criteria may be used to enhance the specificity of the diagnosis: (1) oral temperature higher than 38.3°C, (2) abnormal cervical or vaginal discharge with white cells on saline microscopy (greater than 1 leukocyte per epithelial cell), (3) elevated ESR, (4) elevated CRP, and (5) laboratory documentation of cervical infection with *N gonorrhoeae* or *C trachomatis*. Testing for gonorrhea and chlamydia should be performed. Treatment should not be delayed while awaiting results.

Differential Diagnosis

Appendicitis, ectopic pregnancy, septic abortion, hemorrhagic or ruptured ovarian cysts or tumors, torsion of an ovarian cyst, degeneration of a myoma, and acute enteritis must be considered. PID is more likely to occur when there is a prior history of PID, recent sexual contact, recent onset of menses, recent insertion of an IUD, or recent intercourse with a partner who has a sexually transmitted infection. Acute PID is highly unlikely when recent (within 60 days) intercourse has not taken place. A sensitive serum pregnancy test should be obtained to rule out ectopic pregnancy. Pelvic ultrasonography is helpful to rule out tubo-ovarian abscess. Laparoscopy should be considered when imaging is not informative, and the patient has not responded to outpatient treatment for PID or has not improved after 72 hours of inpatient treatment; it should also be considered when an acutely ill patient has a high suspicion of a competing diagnosis requiring surgical intervention (eg, appendicitis). The appendix should be visualized at laparoscopy to rule out appendicitis. Cultures should be obtained at laparoscopy.

Treatment

A. Antibiotics

Early treatment with appropriate antibiotics effective against *N gonorrhoeae*, *C trachomatis*, and the endogenous organisms listed above is essential to prevent long-term sequelae. The sexual partner should be treated appropriately. Most women with mild to moderate disease can be treated successfully as an outpatient. The recommended outpatient regimen is ceftriaxone (500 mg intramuscularly; 1 g for persons who weigh 150 kg or greater) plus doxycycline (100 mg orally twice a day for 14 days) with metronidazole 500 mg orally twice a day **or** a single dose of cefoxitin (2 g intramuscularly) with probenecid (1 g orally) plus doxycycline (100 mg orally twice daily for 14 days) and metronidazole 500 mg orally twice daily for 14 days. For patients with severe disease or those who meet criteria for hospitalization, there are two recommended regimens. One regimen includes either cefotetan, 2 g intravenously every 12 hours, or cefoxitin, 2 g intravenously every 6 hours or ceftriaxone, 1 g intravenously every 24 hours, plus doxycycline, 100 mg orally or intravenously every 12 hours. The other recommended regimen is clindamycin, 900 mg intravenously every 8 hours, plus gentamicin, a loading dose of 2 mg/kg intravenously or intramuscularly followed by a maintenance dose of 1.5 mg/kg every 8 hours (or as a single daily dose, 3–5 mg/kg). These regimens should be continued for at least 24 hours after the patient shows significant clinical improvement. Then, an oral regimen should be given for a total course of antibiotics of 14 days with doxycycline, 100 mg orally twice a day and metronidazole, 500 mg orally twice a day.

B. Surgical Measures

Surgery is reserved for cases of suspected tubo-ovarian abscess rupture or cases with a poor response to antibiotics. Unless rupture is suspected, the clinician should institute high-dose antibiotic therapy in the hospital, and monitor therapy with ultrasound. In 70% of cases, antibiotics are effective, but in 30%, there is inadequate response in 48–72 hours and surgical intervention is required. Unilateral adnexectomy is acceptable for unilateral abscess. Hysterectomy and bilateral salpingo-oophorectomy may be necessary for overwhelming infection or in cases of chronic disease with intractable pelvic pain.

Prognosis

Despite treatment, long-term sequelae, including repeated episodes of infection, chronic pelvic pain, dyspareunia, ectopic pregnancy, or infertility, develop in one-fourth of women with acute disease. The risk of infertility increases with repeated episodes of salpingitis: it is estimated at 10% after the first episode, 25% after a second episode, and 50% after a third episode.

When to Admit

The following patients with acute PID should be admitted for intravenous antibiotic therapy:

- The patient has a tubo-ovarian abscess (direct inpatient observation for at least 24 hours before switching to outpatient parenteral therapy).
- The patient is pregnant.
- The patient cannot follow or tolerate an outpatient regimen.
- The patient has not responded clinically to outpatient therapy within 72 hours.
- The patient has severe illness, nausea and vomiting, or high fever.
- Another surgical emergency, such as appendicitis, cannot be ruled out.

Curry A et al. Pelvic inflammatory disease: diagnosis, management and prevention. Am Fam Physician. 2019;100:357. [PMID: 31524362]
Ross J et al. 2017 European guideline for the management of pelvic inflammatory disease. Int J STD AIDS. 2018;29:108. [PMID: 29198181]
US Preventive Services Task Force; Krist AH et al. Behavioral counseling interventions to prevent sexually transmitted infections: US Preventive Services Task Force Recommendation Statement. JAMA. 2020;324:674. [PMID: 32809008]
Workowski KA et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70:1. [PMID: 34292926]

CONDYLOMA ACUMINATA

Warty growths on the vulva, perianal area, vaginal walls, or cervix are caused by various types of HPV. Pregnancy and immunosuppression favor growth. Ninety percent of genital warts are caused by HPV 6 and 11. With increasing use of the HPV vaccine in the United States, the prevalence of HPV types 6, 11, 16 and 18 decreased from 11.5% in 2003–2006 to 4.3% in 2009–2012 among girls aged 14–19 years, and from 18.5% to 12.1% in women aged 20–24 years. Vulvar lesions may be obviously wart-like or may be diagnosed only after application of 4% acetic acid (vinegar) and colposcopy, when they appear whitish, with prominent papillae. Vaginal lesions may show diffuse hypertrophy or a cobblestone appearance.

Recommended treatments for vulvar warts include podophyllum resin 10–25% in tincture of benzoin (do not use during pregnancy or on bleeding lesions) or 80–90% trichloroacetic or bichloroacetic acid, carefully applied to avoid the surrounding skin. The pain of bichloroacetic or trichloroacetic acid application can be lessened by a sodium bicarbonate paste applied immediately after treatment. Podophyllum resin must be washed off after 2–4 hours. Freezing with liquid nitrogen or a cryoprobe and electrocautery are also effective. Patient-applied regimens, useful when the entire lesion is accessible to the patient, include podofilox 0.5% solution or gel, imiquimod 5% cream, or sinecatechins 15% ointment. Vaginal warts may be treated with cryotherapy with liquid nitrogen or trichloroacetic acid. Extensive warts may require treatment with CO_2 laser, electrocautery, or excision under local or general anesthesia.

Grennan D. JAMA patient page. Genital warts. JAMA. 2019;321:520. [PMID: 30721297]
Meites E et al. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2019;68:698. [PMID: 31415491]

CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN) (Dysplasia of the Cervix)

ESSENTIALS OF DIAGNOSIS

- The presumptive diagnosis is made by an abnormal Papanicolaou smear.
- Diagnose by colposcopically directed biopsy.

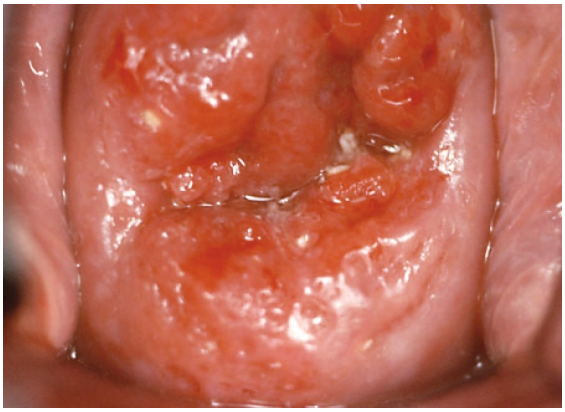
General Considerations

The squamocolumnar junction of the cervix is an area of active squamous cell proliferation. In childhood, this junction is located on the exposed vaginal portion of the cervix. At puberty, because of hormonal influence and possibly because of changes in the vaginal pH, the squamous margin begins to encroach on the single-layered, mucus-secreting epithelium, creating an area of metaplasia (**transformation zone**). Infection with HPV (see Prevention, below) may lead to cellular abnormalities, which over time may develop into squamous cell dysplasia or cancer. There are varying degrees of dysplasia (Table 18–5), defined by the degree of cellular atypia; all atypia must be observed and treated if persistent or worsening.

Table 18–5. Classification systems for Papanicolaou smears.

Dysplasia	CIN	Bethesda System
Benign	Benign	Normal
Benign with inflammation	Benign with inflammation	Normal, ASC-US
Mild dysplasia	CIN I	Low-grade SIL
Moderate dysplasia	CIN II	High-grade SIL
Severe dysplasia	CIN III	High-grade SIL
Carcinoma in situ	—	—
Invasive cancer	Invasive cancer	Invasive cancer

ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; SIL, squamous intraepithelial lesion.



▲ **Figure 18–5.** Erosion of the cervix due to cervical intraepithelial neoplasia (CIN), a precursor lesion to cervical cancer. (Public Health Image Library, CDC.)

Clinical Findings

There are no specific symptoms or signs of CIN. The presumptive diagnosis is made by cytologic screening of an asymptomatic population with no grossly visible cervical changes. All visible abnormal cervical lesions should be biopsied (Figure 18–5).

Screening & Diagnosis

A. Cytologic Examination (Papanicolaou Smear)

In immunocompetent women, cervical cancer screening should begin at age 21. The recommendation to start screening at age 21 years regardless of the age of onset of sexual intercourse is based on the very low incidence of cancer in younger women and the potential for adverse effects associated with treatment of young women with abnormal cytology screening results. In contrast to the high rate of infection with HPV in sexually active adolescents, invasive cervical cancer is very rare in women younger than age 21 years. The USPSTF 2018 statement recommends screening for cervical cancer in women aged 21–65 years as follows: for women aged 21–29 years, screening with cytology (conventional [Papanicolaou smear] or liquid-based) alone every 3 years; and for women aged 30–65 years, screening with cytology alone every 3 years, with high-risk HPV testing alone every 5 years, or with a combination of cytology and high-risk HPV testing (co-testing) every 5 years. These recommendations apply to women who have a cervix, regardless of their sexual history or HPV vaccination status. They do not apply to women who have a previous diagnosis of cervical cancer or a high-grade precancerous cervical lesion (ie, CIN grade II or III), women with immune compromise (eg, living with HIV), or women with in utero exposure to diethylstilbestrol; such women may require more frequent screening.

The USPSTF recommends against screening for cervical cancer for women younger than age 21 years, for women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer, and for women who have had a hysterectomy with removal of the cervix and who have no history of cervical cancer or a high-grade precancerous lesion.

The goal of screening is to identify high-grade precancerous cervical lesions to prevent their progression to cervical cancer. These high-grade cervical lesions may be treated with excisional and ablative therapies. Screening and management guidelines are continually undergoing evaluation and change frequently.

Cytologic reports from the laboratory may describe findings in one of several ways (see Table 18–5). The Bethesda System uses the terminology "atypical squamous cells of unknown significance" (**ASC-US**) and "squamous intraepithelial lesions," either low-grade (**LSIL**) or high-grade (**HSIL**). HPV DNA testing can be used adjunctively as a triage test to stratify risk in women age 21 years and older with a cytologic diagnosis of ASC-US and in postmenopausal women with a cytologic diagnosis of ASC-US or LSIL.

Women with ASC-US and a negative HPV screening may be followed up in 1 year with a repeat Papanicolaou smear and HPV co-testing. If the HPV screen is positive, colposcopy is indicated. If HPV screening is unavailable, repeat cytology may be done at 12 months. Women aged 21–24 with low-grade squamous intraepithelial lesion (LSIL) should have repeat Papanicolaou smear in 1 year. Women aged 25 or older with squamous intraepithelial lesion (SIL) or atypical glandular cells should undergo colposcopy. For the most current guidelines, please consult these sources: https://www.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/cervical-cancer-screening (August 2018) and https://www.asccp.org/guidelines (April 2019).

Chor J et al. Cervical cancer screening guideline for individuals at average risk. JAMA. 2021;326:2193. [PMID: 34766970]

B. Colposcopy

Women who have positive HPV screening or women aged 25 or older with squamous intraepithelial lesion or atypical glandular cells should be referred for colposcopy. Viewing the cervix with 10–20 × magnification allows for assessment of the size and margins of an abnormal transformation zone and determination of extension into the endocervical canal. The application of 3–5% acetic acid (vinegar) dissolves mucus, and the acid's desiccating action sharpens the contrast between normal and actively proliferating squamous epithelium. Abnormal changes include white patches and vascular atypia, which indicate areas of greatest cellular activity.

C. Biopsy

Colposcopically directed biopsy and endocervical curettage are office procedures. Data from both cervical biopsy and endocervical curettage are important in deciding on treatment.

Prevention

Virtually all cervical dysplasias and cancers are associated with cervical infection with HPV. There are over 100

recognized HPV subtypes. Types 6 and 11 tend to cause genital warts and mild dysplasia and rarely progress to cervical cancer; types 16, 18, 31, and others cause higher-grade dysplasia. The HPV 9-valent (Gardasil-9) recombinant vaccine (9vHPV) is indicated for the prevention of cervical, vaginal, and vulvar cancers (in women) and anal cancers (in women and men) caused by HPV types 16, 18, 31, 33, 45, 52, and 58; genital warts (in women and men) caused by HPV types 6 and 11; and precancerous/dysplastic lesions of cervix, vagina, vulva (in women), and anus (in women and men) caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Gardasil-9 is recommended for vaccination of females and males aged 9–45 years old. The earlier HPV 4-valent vaccine known as Gardasil that was indicated for prevention of diseases related to HPV types 6, 11, 16, and 18 has been discontinued in the United States. The use of HPV vaccination in the United States continues to increase; however, the HPV vaccination continues to lag far behind other vaccines recommended for adolescents. In 2018, 51% of adolescents were up to date with the three-dose HPV vaccine series compared with 48% in 2017.

Because complete coverage of all carcinogenic HPV types is not provided by either vaccine, all women need to have regular cervical cancer screening as outlined above. In addition to vaccination, preventive measures include limiting the number of sexual partners and thus exposure to HPV, using a condom for coitus, smoking cessation, and avoiding exposure to secondhand smoke.

Treatment

Treatment varies depending on the degree and extent of CIN. Biopsies should precede treatment, except in cases of high-grade squamous intraepithelial lesion (HSIL) where it may be appropriate to proceed directly to a LEEP.

A. Cryosurgery

The use of freezing (cryosurgery) is effective for noninvasive small lesions visible on the cervix without endocervical extension.

B. CO_2 Laser

This well-controlled method minimizes tissue destruction. It is colposcopically directed and requires special training. It may be used with large visible lesions and involves vaporization of the transformation zone on the cervix and the distal 5–7 mm of endocervical canal.

C. Loop Excision

When the CIN is clearly visible in its entirety, a wire loop can be used for excisional biopsy. This office procedure, called **LEEP (loop electrosurgical excision procedure)**, done with local anesthesia is quick and straightforward. Cutting and hemostasis are achieved with a low-voltage electrosurgical machine.

D. Conization of the Cervix

Conization is surgical removal of the entire transformation zone and endocervical canal. It typically is reserved for cases of severe dysplasia (CIN III) or carcinoma in situ, particularly those with endocervical extension. It can be performed with scalpel, CO_2 laser, needle electrode, or large-loop excision.

Follow-Up

Because recurrence is possible—especially in the first 2 years after treatment—and because the false-negative rate of a single cervical cytologic test is 20%, close follow-up after colposcopy and biopsy is imperative. Following excisional or ablative procedure, HPV-based testing should be performed at 6 months and then annually for 3 years followed by HPV-based testing every 3 years for at least 25 years. Colposcopy and endocervical sampling should be performed for any abnormality.

The American Society for Colposcopy and Cervical Pathology Guidelines for cervical cancer screening and management of abnormal Papanicolaou smears are available online (https://www.asccp.org/guidelines).

When to Refer

- Patients with CIN II/III should be referred to an experienced colposcopist.
- Patients requiring conization biopsy should be referred to a gynecologist.

Chor J et al. Cervical cancer screening guideline for individuals at average risk. JAMA. 2021;326:2193. [PMID: 34766970]
Kalliala I et al. Incidence and mortality from cervical cancer and other malignancies after treatment of cervical intraepithelial neoplasia: a systematic review and meta-analysis of the literature. Ann Oncol. 2020;31:213. [PMID: 31959338]
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Perkins RB et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2020;24:102. [PMID: 32243307]
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CARCINOMA OF THE CERVIX

ESSENTIALS OF DIAGNOSIS

- Increased risk in women who smoke and those with HIV or high-risk HPV types.
- Gross lesions should be evaluated by colposcopically directed biopsies and not cytology alone.

General Considerations

Cervical cancer is the third most common cancer in the world and the leading cause of cancer death among women in developing countries. It is considered a sexually

transmitted infection as both squamous cell and adenocarcinoma of the cervix are secondary to infection with HPV, primarily types 16 and 18. Women infected with HIV and with other forms of immunosuppression are at an increased risk for high-risk HPV infection and CIN. Smoking appears to be a cofactor for squamous cell carcinoma (SCC). SCC accounts for approximately 80% of cervical cancers, while adenocarcinoma accounts for 15%, and adenosquamous carcinoma for 3–5%; neuroendocrine or small cell carcinomas are rare.

SCC appears first in the intraepithelial layers (the preinvasive stage, or carcinoma in situ). Preinvasive cancer (CIN III) is most commonly diagnosed in women 25–35 years of age. Two to 10 years are required for carcinoma to penetrate the basement membrane and become invasive. While cervical cancer mortality has declined steadily in the United States due to high rates of screening and improved treatment, the rate of decline has slowed in recent years. In general, Black women experienced much higher incidence and mortality than White women. The 5-year survival rate ranges from 73% for stage II cervical cancer to less than 20% for stage IV.

Clinical Findings

A. Symptoms and Signs

Early cervical cancer is often asymptomatic. The most common signs are irregular or heavy bleeding and postcoital spotting. Bladder and rectal dysfunction or fistulas and pain are late sequelae.

B. Cervical Biopsy and Endocervical Curettage or Conization

These procedures are necessary steps after a positive Papanicolaou smear to determine the extent and depth of invasion of the cancer. Even if the smear is positive, definitive diagnosis must be established through biopsy before additional treatment is given.

C. "Staging" or Estimate of Gross Spread of Cancer of the Cervix

Staging of invasive cervical cancer is achieved by clinical evaluation, usually conducted under anesthesia. Further examinations, such as ultrasonography, CT, MRI, lymphangiography, laparoscopy, and fine-needle aspiration, are valuable for treatment planning.

Complications

Metastases to regional lymph nodes occur with increasing frequency from stage I to stage IV. Paracervical extension occurs in all directions from the cervix. The ureters may become obstructed lateral to the cervix, causing hydroureter and hydronephrosis and consequently impaired kidney function. Almost two-thirds of patients with untreated carcinoma of the cervix die of uremia when ureteral obstruction is bilateral. Pain in the back, in the distribution of the lumbosacral plexus, is often indicative of neurologic involvement. Gross edema of the legs may be indicative of vascular and lymphatic stasis due to tumor. Vaginal fistulas to the rectum and urinary tract are severe late complications. Hemorrhage causes death in 10–20% of patients with extensive invasive carcinoma.

Prevention

Vaccination with the recombinant 9-valent HPV vaccine (Gardasil-9) can prevent cervical cancer by targeting the HPV types that pose the greatest risk and protect against low-grade and precancerous lesions caused by other HPV types (see Cervical Intraepithelial Neoplasia).

Treatment

A. Emergency Measures

Vaginal hemorrhage originates from gross ulceration and cavitation in later stage cervical carcinoma. Ligation and suturing of the cervix are usually not feasible, but emergent vaginal packing, cautery, tranexamic acid, and irradiation are helpful to stop bleeding temporarily. Ligation, resection, or embolization of the uterine or hypogastric arteries may be lifesaving when other measures fail.

B. Specific Measures

1. Carcinoma in situ (stage 0)—In women for whom childbearing is not a consideration, total hysterectomy is the definitive treatment. In women who wish to retain the uterus, acceptable alternatives include cryosurgery, laser surgery, LEEP, or cervical conization. HPV-based testing should be repeated at 6 months and then annually for 3 years followed by HPV-based testing every 3 years for at least 25 years.

2. Invasive carcinoma—Microinvasive carcinoma (stage IA1) is treated with simple, extrafascial hysterectomy. Stages IA2 and IB1 cancers are typically treated with modified radical hysterectomy and pelvic lymphadenectomy. Women with stage IB1 may be candidates for fertility-sparing surgery, which includes radical trachelectomy and lymph node dissection with preservation of the uterus and ovaries. Women with IB2 cancers typically undergo radical hysterectomy and pelvic lymphadenectomy. Adjuvant chemotherapy or radiation may be used for women with risk factors for recurrence. Women with locally advanced disease (stage IB3 to IVA) usually are treated with primary chemoradiation. Metastatic disease (stage IVB) typically is treated with chemotherapy.

Prognosis

The overall 5-year relative survival rate for carcinoma of the cervix is 68% in White women and 55% in Black women in the United States. Survival rates are inversely proportionate to the stage of cancer: stage 0, 99–100%; stage IA, more than 94%; stage IB–IIA, 73–90%; stage IIB, 65%; stage III, 40%; and stage IV, less than 20%.

When to Refer

All patients with invasive cervical carcinoma (stage IA or higher) should be referred to a gynecologic oncologist.

American Cancer Society. Survival rates for cervical cancer, by stage, January 3, 2020. https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/survival.html
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Stolnicu S et al. Recent advances in invasive adenocarcinoma of the cervix. Virchows Arch. 2019;475:537. [PMID: 31209635]
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CARCINOMA OF THE ENDOMETRIUM

ESSENTIALS OF DIAGNOSIS

- AUB is the presenting sign in 90% of cases.
- After a negative pregnancy test, endometrial tissue is required to confirm the diagnosis.

General Considerations

Adenocarcinoma of the endometrium is the most common cancer of the female genital tract in developed countries. It occurs most often in women 50–70 years of age. Obesity, nulliparity, diabetes mellitus, polycystic ovaries with prolonged anovulation, unopposed estrogen therapy, and the extended use of tamoxifen for the treatment of breast cancer are risk factors. Women with a family history of colon cancer (hereditary nonpolyposis colorectal cancer, Lynch syndrome) are at significantly increased risk, with a lifetime incidence as high as 30%.

Abnormal bleeding is the presenting sign in 90% of cases. Any postmenopausal bleeding requires investigation. Pain generally occurs late in the disease, with metastases or infection.

Papanicolaou smear of the cervix occasionally shows atypical endometrial cells but is an insensitive diagnostic tool. Endocervical and endometrial sampling is the only reliable means of diagnosis and is important to differentiate endometrial cancer from hyperplasia, which often can be treated hormonally. Simultaneous hysteroscopy can be a valuable addition to localize polyps or other lesions within the uterine cavity. Pelvic ultrasonography may determine the thickness of the endometrium as an indication of hypertrophy and possible neoplastic change. The finding of a thin endometrial lining on ultrasound (4 mm or less) in a postmenopausal woman is clinically reassuring in cases where very little tissue is obtainable through endometrial biopsy.

Prevention

Prompt endometrial sampling for patients who report abnormal menstrual bleeding or postmenopausal uterine bleeding will reveal many incipient and clinical cases of endometrial cancer. Younger women with chronic anovulation are at risk for endometrial hyperplasia and subsequent endometrial cancer; they can significantly reduce the risk of hyperplasia with the use of oral contraceptives, cyclic progestin therapy, or a hormonal IUD.

Staging

Staging and prognosis are based on surgical and pathologic evaluation only. Examination under anesthesia, endometrial and endocervical sampling, chest radiography, intravenous urography, cystoscopy, sigmoidoscopy, transvaginal sonography, and MRI will help determine the extent of the disease and its appropriate treatment.

Treatment

Treatment consists of total hysterectomy and bilateral salpingo-oophorectomy. Peritoneal washings for cytologic examination are routinely taken and lymph node sampling may be done. Women with high-risk endometrial cancer (serous adenocarcinoma, clear cell carcinoma, grade 3 deeply invasive endometrioid carcinoma, and stages III/IV disease) are generally treated with surgery followed by chemotherapy and/or radiation therapy.

Prognosis

With early diagnosis and treatment, the overall 5-year survival for stage I disease is 80–90%. With stage I disease, the depth of myometrial invasion is the strongest predictor of survival, with a 90% 5-year survival with less than 50% depth of invasion and 80% survival with 50% or more invasion. Survival rates decrease with increasing stage of disease.

When to Refer

All patients with endometrial carcinoma should be referred to a gynecologic oncologist.

Chargari C et al. Brachytherapy: an overview for clinicians. CA Cancer J Clin. 2019;69:386. [PMID: 31361333]
Cusimano MC et al. Laparoscopic and robotic hysterectomy in endometrial cancer patients with obesity: a systematic review and meta-analysis of conversions and complications. Am J Obstet Gynecol. 2019;221:410. [PMID: 31082383]
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CARCINOMA OF THE VULVA

ESSENTIALS OF DIAGNOSIS

- Two independent pathways for development: HPV or chronic inflammation.
- History of prolonged vulvar irritation, with pruritus, local discomfort, or slight bloody discharge.
- Early lesions may suggest or include non-neoplastic epithelial disorders.

- Late lesions appear as a mass, an exophytic growth, or a firm, ulcerated area in the vulva.
- Biopsy is necessary for diagnosis.

General Considerations

Most cancers of the vulva are squamous lesions that classically occur in women over 50. Vulvar low-grade squamous intraepithelial lesions (LSIL) are benign and do not require intervention. Vulvar high-grade squamous intraepithelial lesions (HSIL) and differentiated vulvar intraepithelial neoplasia (dVIN) are premalignant conditions. Vulvar HSIL (VIN usual type) is associated with HPV, while dVIN is associated with vulvar dermatoses, eg, lichens sclerosus. About 70–90% of premalignant lesions are vulvar HSIL, but HSIL is the precursor for only 20% of vulvar cancers, while dVIN is the precursor for approximately 80% of vulvar cancers. Given that high percentages of HSIL and vulvar cancers are HPV-related, immunization with the HPV vaccine is beneficial to reduce the risk of HPV-related vulvar disease.

Differential Diagnosis

Other vulvar lesions must be considered. Vulvar intraepithelial neoplasia may resemble vulvar cancer and must be distinguished by histology. Benign vulvar disorders that must be excluded in the diagnosis of carcinoma of the vulva include inflammatory vulvar dermatoses (psoriasis, lichen sclerosus, lichen planus), chronic granulomatous lesions (eg, lymphogranuloma venereum, syphilis), condylomas, epidermal inclusion cysts, hidradenomas, or neurofibromas. Lichen sclerosus and other associated leukoplakic changes in the skin should be biopsied. The likelihood that a superimposed vulvar cancer will develop in a woman with a non-neoplastic epithelial disorder is low (1–5%).

Diagnosis

Biopsy is essential for the diagnosis of VIN and vulvar cancer and should be performed with any localized atypical vulvar lesion, including white patches and hyperpigmented lesions. Multiple skin-punch specimens can be taken in the office under local anesthesia, with care to include tissue from the edges of each lesion sampled. Colposcopy of vulva, vagina, and cervix can help in identifying areas for biopsy and in planning further treatment.

Staging

Vulvar cancer generally spreads by direct extension into the vagina, urethra, perineum, and anus, with discontinuous spread into the inguinal and femoral lymph nodes. Staging is based on a combined clinical and surgical/pathologic system.

Treatment

Invasive carcinoma confined to the vulva without evidence of spread to adjacent organs or to the regional lymph nodes is treated with wide local excision and inguinal lymphadenectomy or wide local excision alone if invasion is less than 1 mm. To avoid the morbidity of inguinal lymphadenectomy, some guidelines recommend sentinel lymph node sampling for women with early-stage vulvar cancer. Patients with more advanced disease may receive preoperative radiation, chemotherapy, or both.

Prognosis

Vulvar squamous cell carcinomas seldom metastasize. With adequate excision, the prognosis is excellent. Patients with invasive vulvar SCC 2 cm in diameter or less, without inguinal lymph node metastases, have an 85–90% 5-year survival rate. If the lesion is larger than 2 cm and lymph node involvement is present, the likelihood of 5-year survival is approximately 40%.

When to Refer

All patients with invasive vulvar carcinoma should be referred to a gynecologic oncologist.

Gadducci A et al. Locally advanced squamous cell carcinoma of the vulva: a challenging question for gynecologic oncologists. Gynecol Oncol. 2020;158:208. [PMID: 32460996]
Morrison J et al. British Gynaecological Cancer Society (BGCS) vulval cancer guidelines: recommendations for practice. Eur J Obstet Gynecol Reprod Biol. 2020;252:502. [PMID: 32620514]
Singh N et al. Vulval squamous cell carcinoma and its precursors. Histopathology. 2020;76:128. [PMID: 31846523]
Tan A et al. Diagnosis and management of vulvar cancer: a review. J Am Acad Dermatol. 2019;81:1387. [PMID: 31349045]

OVARIAN TUMORS & OVARIAN CANCER

ESSENTIALS OF DIAGNOSIS

- Symptoms include vague GI discomfort, pelvic pressure, or pain.
- Many cases of early-stage cancer are asymptomatic.
- Pelvic examination and ultrasound are mainstays of diagnosis.

General Considerations

Ovarian tumors are common. Most are benign, but malignant ovarian tumors are the leading cause of death from gynecologic cancer. The wide range of types and patterns of ovarian tumors is due to the complexity of ovarian embryology and differences in tissues of origin.

In women with no family history of ovarian cancer, the lifetime risk in the United States is 1.3%, whereas a woman with one affected first-degree relative has a 5% lifetime risk. Worldwide, the risk of ovarian cancer is 2.7%. Ultrasound or tumor marker screening for women with one or no affected first-degree relatives has not been shown to reduce mortality from ovarian cancer, and the

risks associated with unnecessary prophylactic surgical procedures outweigh the benefits in low-risk women. With two or more affected first-degree relatives, the risk is 7%. Approximately 3% of women with two or more affected first-degree relatives will have a **hereditary ovarian cancer syndrome** with a lifetime ovarian cancer risk of 40%. Women with a *BRCA1* gene pathogenic variant have a 45% lifetime risk of ovarian cancer and those with a *BRCA2* pathogenic variant, a 25% risk. Consideration should be given to screening with transvaginal sonography and serum CA 125 testing, starting at age 30–35 years for women with *BRCA1* pathogenic variant or age 35–40 for women with *BRCA2* pathogenic variant or 5–10 years earlier than the earliest age that ovarian cancer was first diagnosed in any family member. Of note, this screening regimen has not been shown to reduce mortality; thus, prophylactic oophorectomy should be considered at conclusion of childbearing.

Clinical Findings

A. Symptoms and Signs

Most women with both benign and malignant ovarian neoplasms are either asymptomatic or experience only mild nonspecific GI symptoms or pelvic pressure. Women with advanced malignant disease may experience abdominal pain and bloating, and a palpable abdominal mass with ascites is often present.

B. Laboratory Findings

Serum CA 125 is elevated in 80% of women with epithelial ovarian cancer overall but in only 50% of women with early disease. However, CA 125 may be elevated in premenopausal women with benign disease (such as endometriosis), minimizing its usefulness in ovarian cancer screening. In premenopausal women with ovarian masses, other tumor markers (such as human chorionic gonadotropin [hCG], LD, or alpha-fetoprotein) may be indicators of the tumor type.

C. Imaging

Transvaginal sonography is useful for screening high-risk women but has inadequate sensitivity for screening low-risk women. Ultrasound is helpful in differentiating ovarian masses that are benign and likely to resolve spontaneously from those with malignant potential. Color Doppler imaging may further enhance the specificity of ultrasound diagnosis.

Differential Diagnosis

Once an ovarian mass has been detected, it must be categorized as functional, benign neoplastic, or potentially malignant. Predictive factors include age, size of the mass, ultrasound configuration, serum CA 125 level, the presence of symptoms, and whether the mass is unilateral or bilateral. Simple cysts up to 10 cm in diameter are almost universally benign in both premenopausal and postmenopausal patients. Most will resolve spontaneously and may be monitored without intervention. If the mass is larger or unchanged on repeat transvaginal sonography, or if symptomatic, surgical evaluation is warranted.

Treatment

If a malignant ovarian mass is suspected, surgical evaluation should be performed by a gynecologic oncologist. For benign neoplasms, tumor excision or unilateral oophorectomy is usually performed. For ovarian cancer in an early stage, the standard therapy is complete surgical staging including hysterectomy and bilateral salpingo-oophorectomy with omentectomy and selective lymphadenectomy. With more advanced disease, aggressive removal of all visible tumor improves survival. Except for women with low-grade ovarian cancer in an early stage, postoperative chemotherapy is indicated (see Table 39–3). Several chemotherapy regimens are effective, such as the combination of cisplatin or carboplatin with paclitaxel, with clinical response rates of up to 60–70%.

Prognosis

Advanced disease is diagnosed in approximately 75% of women with ovarian cancer. The overall 5-year survival is approximately 17% with distant metastases but is 89% with early-stage disease.

When to Refer

If a malignant mass is suspected, surgical evaluation should be performed by a gynecologic oncologist.

Centers for Disease Control and Prevention (CDC). Ovarian cancer screening. 2021. https://www.cdc.gov/cancer/ovarian/basic_info/screening.htm

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González-Martín A et al. Immunotherapy with checkpoint inhibitors in patients with ovarian cancer: still promising? Cancer. 2019;125:4616. [PMID: 31967676]

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19 Obstetrics & Obstetric Disorders

Vanessa L. Rogers, MD
Scott W. Roberts, MD

DIAGNOSIS OF PREGNANCY

It is advantageous to diagnose pregnancy as promptly as possible. Prenatal care can begin early for a desired pregnancy, and potentially harmful medications and activities such as drug and alcohol use, smoking, and occupational chemical exposure can be eliminated. If an unwanted pregnancy occurs, counseling about options can be provided at an early stage.

Pregnancy Tests

All urine or blood pregnancy tests rely on the detection of human chorionic gonadotropin (hCG) produced by the placenta. Levels increase shortly after implantation, approximately double every 48 hours (this rise can range from 30% to 100% in normal pregnancies), reach a peak at 50–75 days, and fall to lower levels in the second and third trimesters. Pregnancy tests are performed on serum or urine and are accurate at the time of the missed period or shortly after it.

Compared with intrauterine pregnancies, **ectopic pregnancies** may show lower levels of hCG that plateau or fall in serial determinations. Quantitative assays of hCG repeated at 48-hour intervals are used in the diagnosis of ectopic pregnancy as well as in cases of molar pregnancy and early pregnancy loss. Comparison of hCG levels between laboratories may be misleading in a given patient because different international standards may produce results that vary by as much as twofold. Consistent follow-up is necessary to make the correct diagnosis and management plan. **Pregnancy of unknown location** is a term used to describe a situation where a woman has a positive pregnancy test, but the location and viability of the pregnancy are not known because it is not seen on transvaginal ultrasound.

Manifestations of Pregnancy

The following symptoms and signs are usually due to pregnancy, but none are diagnostic. A record of the time of coitus or insemination is helpful for diagnosing and dating a pregnancy.

A. Symptoms

Amenorrhea, nausea and vomiting, breast tenderness and tingling, urinary frequency and urgency, "quickening" (perception of first movement noted at about the 18th week), weight gain.

B. Signs (in Weeks From Last Menstrual Period)

Breast changes (enlargement, vascular engorgement, colostrum) begin early in pregnancy and continue until the postpartum period. Cyanosis of the vagina and cervical portio and softening of the cervix occur in about the 7th week. Softening of the cervicouterine junction takes place in the 8th week, and generalized enlargement and diffuse softening of the corpus occurs after the 8th week. When a woman's abdomen will start to enlarge depends on her body habitus but typically starts in the 16th week.

The uterine fundus is palpable above the pubic symphysis by 12–15 weeks from the last menstrual period and reaches the umbilicus by 20–22 weeks. Fetal heart tones can be heard by Doppler at 10–12 weeks' gestation.

Differential Diagnosis

The nonpregnant uterus enlarged by myomas can be confused with the gravid uterus, but it is usually firm and irregular. An ovarian tumor may be found midline, displacing the nonpregnant uterus to the side or posteriorly. Ultrasonography and a pregnancy test will provide accurate diagnosis in these circumstances.

ESSENTIALS OF PRENATAL CARE

Prenatal visits should begin as early as possible after the diagnosis of pregnancy. The initial visit should include a history, physical examination, advice to the patient, and appropriate tests and procedures (see *CMDT Online* at AccessMedicine.com for a discussion of routine prenatal care).

A. Medications

Only medications prescribed or authorized by the obstetric provider should be taken since certain medications are contraindicated during pregnancy (Table 19–1).

Table 19–1. Common drugs that are teratogenic or fetotoxic.[1]

ACE inhibitors	Lithium
Alcohol	Methotrexate
Androgens	Misoprostol
Angiotensin-II receptor blockers	NSAIDs (third trimester)
Antiepileptics (phenytoin, valproic acid, carbamazepine)	Opioids (prolonged use)
Benzodiazepines	Radioiodine (antithyroid)
Cyclophosphamide	Reserpine
Diazoxide	Ribavirin
Diethylstilbestrol	Sulfonamides (second and third trimesters)
Disulfiram	Tetracycline (third trimester)
Ergotamine	Thalidomide
Estrogens	Tobacco smoking
Griseofulvin	Warfarin and other coumarin anticoagulants
Isotretinoin	

[1]Many other drugs are also contraindicated during pregnancy. Evaluate any drug for its need versus its potential adverse effects. Further information can be obtained from the manufacturer or from any of several teratogenic registries around the country. Go to https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm for more information.

B. Alcohol and Other Drugs

Pregnant women should be encouraged to abstain from alcohol, tobacco, and all recreational ("street") drugs. No safe level of alcohol intake has been established for pregnancy. Fetal effects are manifest in the **fetal alcohol syndrome,** which includes growth restriction; facial, skeletal, and cardiac abnormalities; and serious CNS dysfunction.

Cigarette smoking results in fetal exposure to carbon monoxide and nicotine, which may eventuate to adverse pregnancy outcomes. An increased risk of placental abruption (abruptio placentae), placenta previa, and premature rupture of the membranes is documented among women who smoke. Preterm delivery, low birth weight, and ectopic pregnancy are also more likely among cigarette smokers. Women who smoke should quit smoking or at least reduce the number of cigarettes smoked per day to as few as possible. Complete cessation is preferred over reduction with the best outcomes seen in women who stop smoking prior to 15 weeks' gestation. Clinicians should ask all pregnant women about their smoking history and offer smoking cessation counseling during pregnancy, since women are more motivated to change at this time. Pregnant women should also avoid exposure to environmental smoke ("passive smoking"), smokeless tobacco, and e-cigarettes. Pharmacotherapy for smoking cessation has been used with mixed results. Studies of bupropion and nicotine replacement systems are inadequate to properly weigh risks and benefits.

Sometimes compounding the above effects on pregnancy outcome are the independent adverse effects of illicit drugs. Cocaine use in pregnancy is associated with an increased risk of premature rupture of membranes, preterm delivery, placental abruption, intrauterine growth restriction, neurobehavioral deficits, and sudden infant death syndrome. Similar adverse effects on pregnancy are associated with amphetamine use, perhaps reflecting the vasoconstrictive properties of both amphetamines and cocaine. Adverse effects associated with opioid use include intrauterine growth restriction, prematurity, and fetal death. For pregnant women with opioid use disorder, opioid agonist therapy is the standard of care (see Chapter 5).

C. Radiographs and Noxious Exposures

Radiographs should be avoided unless essential and approved by a clinician. Abdominal shielding should be used whenever possible. The patient should be told to inform her other health care providers that she is pregnant. Chemical or radiation hazards should be avoided as should excessive heat in hot tubs or saunas. Patients should be told to avoid handling cat feces or cat litter and to wear gloves when gardening to avoid infection with toxoplasmosis.

LACTATION

Drugs taken by a nursing mother may accumulate in milk and be transmitted to the infant (Table 19–2). The amount of drug entering the milk depends on the drug's lipid solubility, mechanism of transport, and degree of ionization.

Sattari M et al. Maternal implications of breastfeeding: a review for the internist. Am J Med. 2019;132:912. [PMID: 30853481]

TRAVEL & IMMUNIZATIONS DURING PREGNANCY

During an otherwise normal low-risk pregnancy, travel can be planned most safely up to the 32nd week. Commercial flying in pressurized cabins does not pose a threat to the fetus. An aisle seat will allow frequent walks. Adequate fluids should be taken during the flight. Travel can also increase women's chances of exposure to SARS-CoV-2, the virus that causes COVID-19. Pregnant women infected with SARS-CoV-2 are believed to be at increased risk for preterm birth and for serious illness compared with women who are not pregnant. Pregnant women should limit their exposure to people outside their household, wear a mask while outside the home, practice frequent hand washing, and social distance.

Vaccination against COVID-19 is recommended for women who are pregnant, trying to get pregnant, or may become pregnant, and who are breastfeeding. The CDC has determined that the benefits of vaccination outweigh any risks. There is no evidence that vaccination causes problems with fertility in men or women. Pregnant women who have been vaccinated may receive the COVID-19 booster shot. There have been rare reports of thrombosis with thrombocytopenia syndrome in women younger than 50 years old who received the Johnson and Johnson's Janssen vaccine. This risk has not been found with the Pfizer-BioNTech and Moderna vaccines; women younger than 50 years old with access to multiple vaccines may want to factor this into their decision-making process.

Traveling to endemic areas of yellow fever (Africa or Latin America) or of Zika virus (Latin America) is not advisable; since Zika virus can be sexually transmitted,

Table 19–2. Drugs and substances that require a careful assessment of risk before they are prescribed for breastfeeding women.[1]

Drugs	Concern
Atenolol	Hypotension and bradycardia in the infant. Metoprolol and propranolol are preferred.
Ciprofloxacin	Adverse effects on fetal cartilage and bone. Must weigh risks versus benefits.
Codeine, oxycodone	CNS depression. Unpredictable metabolism.
Cyclophosphamide	Neonatal neutropenia. No breastfeeding.
Diphenhydramine	Present in small quantities in milk; sources are conflicting regarding its safety.
Fluoxetine	Present in breast milk in higher levels than other SSRIs. Watch for adverse effects like an infant's fussiness and crying.
Lisinopril	Unknown effects. Captopril or enalapril is preferred if an ACE inhibitor is needed.
Lithium	Circulating levels in the neonate are variable. Follow infant's serum creatinine and BUN levels and thyroid function tests.
Tetracyclines	Adverse effects on fetal bone growth and dental staining.
Valproic acid	Long-term effects are unknown. Although levels in milk are low, it is teratogenic, so it should be avoided if possible.

[1]The above list is not all-inclusive. For additional information, see the reference from which this information is adapted: Rowe H et al. Maternal medication, drug use, and breastfeeding. Pediatr Clin North Am. 2013;60:275, or the online drug and lactation database, Lactmed, at https://www.ncbi.nlm.nih.gov/books/NBK501922/.

partner travel should also be discussed (see Chapter 32). Similarly, it is inadvisable to travel to areas of Africa or Asia where chloroquine-resistant falciparum malaria is a hazard, since complications of malaria are more common in pregnancy.

Ideally, all immunizations should precede pregnancy. *Live virus products are contraindicated during pregnancy (measles, rubella, yellow fever, and smallpox).* Inactivated polio vaccine should be given subcutaneously instead of the oral live-attenuated vaccine. The varicella vaccine should be given 1–3 months before becoming pregnant. It is not recommended in pregnancy. Vaccines against pneumococcal pneumonia, meningococcal meningitis, and hepatitis A can be used as indicated. Pregnant women who are high risk for hepatitis B and who have not been previously vaccinated should be vaccinated during pregnancy. The HPV vaccine is not recommended for pregnant women. However, adverse outcomes have not been described when used during pregnancy. If a woman who has started the vaccine series is pregnant, the remaining doses should be administered when she is no longer pregnant.

The CDC lists pregnant women as a high-risk group for influenza. Annual influenza vaccination is indicated in all women who are pregnant or will be pregnant during the "flu season." It can be given in the first trimester. The CDC also recommends that every pregnant woman receive a dose of Tdap during each pregnancy irrespective of her prior vaccination history. The optimal timing for such Tdap administration is between 27 and 36 weeks' gestation, to maximize the antibody response of the pregnant woman against pertussis and the passive antibody transfer to the infant. For any woman who was not previously vaccinated with Tdap and for whom the vaccine was not given during her pregnancy, Tdap should be administered immediately postpartum. Further, any teenagers or adults not previously vaccinated who will have close contact with the infant should also receive it, ideally 2 weeks before exposure to the child. This vaccination strategy is called "cocooning," and its purpose is to protect the infant aged younger than 12 months who is at particularly high risk for lethal pertussis.

Hepatitis A vaccine contains formalin-inactivated virus and can be given in pregnancy when needed. Pooled immune globulin to prevent hepatitis A is safe and does not carry risk of HIV transmission. Chloroquine can be used for malaria prophylaxis in pregnancy, and proguanil is also safe.

Water should be purified by boiling in settings where there is potential for microbial contamination, since iodine purification may provide more iodine than is safe during pregnancy.

Prophylactic antibiotics or bismuth subsalicylate should not be used during pregnancy to prevent diarrhea. Oral rehydration and treatment of bacterial diarrhea with erythromycin or ampicillin if necessary is preferred.

Centers for Disease Control and Prevention. COVID-19 Vaccines While Pregnant or Breastfeeding. 2021 Dec 6. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html

OBSTETRIC COMPLICATIONS OF THE FIRST & SECOND TRIMESTERS

VOMITING OF PREGNANCY & HYPEREMESIS GRAVIDARUM

ESSENTIALS OF DIAGNOSIS

- **Hyperemesis gravidarum**
  - Persistent, severe vomiting.
  - Weight loss, dehydration, hypochloremic alkalosis, hypokalemia.

- May have transient elevation of liver enzymes.
- Appears related to high or rising serum hCG.

▶ More common with multifetal pregnancies or hydatidiform mole.

General Considerations

Nausea and vomiting begin soon after the first missed period and cease by the fifth month of gestation. Up to three-fourths of women complain of nausea and vomiting during early pregnancy, with the vast majority noting nausea throughout the day. This problem exerts no adverse effects on the pregnancy and does not presage other complications.

Persistent, severe vomiting during pregnancy—hyperemesis gravidarum—can be disabling and require hospitalization. Hyperthyroidism can be associated with hyperemesis gravidarum, so it is advisable to determine TSH and free thyroxine (FT_4) values in these patients.

Treatment

A. Mild Nausea and Vomiting of Pregnancy

In most instances, only reassurance and dietary advice are required. Because of possible teratogenicity, drugs used during the first half of pregnancy should be restricted to those of major importance to life and health. Pyridoxine (vitamin B_6), 50–100 mg/day orally, is nontoxic and may be helpful in some patients. Pyridoxine alone or in combination with doxylamine (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, two tablets at bedtime) is first-line pharmacotherapy. Antiemetics, antihistamines, and antispasmodics are generally unnecessary.

B. Hyperemesis Gravidarum

With more severe nausea and vomiting, it may become necessary to hospitalize the patient. In this case, a private room with limited activity is preferred. It is recommended to give nothing by mouth until the patient is improving, and maintain hydration and electrolyte balance by giving appropriate parenteral fluids and vitamin supplements as indicated. Antiemetics such as promethazine (12.5–25 mg orally, rectally, or intravenously every 4–6 hours), metoclopramide (5–10 mg orally or intravenously every 6 hours), or ondansetron (4–8 mg orally or intravenously every 8 hours) should be started. Ondansetron has been associated in some studies with congenital anomalies. Data are limited, but the risks and benefits of treatment should be addressed with the patient. If there is an increased risk, it is probably low. Antiemetics will likely need to be given intravenously initially. Rarely, total parenteral nutrition may become necessary but only if enteral feedings cannot be done. As soon as possible, the patient should be placed on a dry diet consisting of six small feedings daily. Antiemetics may be continued orally as needed. After inpatient stabilization, the patient can be maintained at home even if she requires intravenous fluids in addition to her oral intake. There are conflicting studies regarding the use of corticosteroids for the control of hyperemesis gravidarum, and it has also been associated with fetal anomalies, specifically oral clefts. The increase in risk is likely small. However, this treatment should be withheld before 10 weeks' gestation and until more accepted treatments have been exhausted.

When to Refer

- Patient does not respond to first-line outpatient management.
- There is concern for other pathology (ie, hydatidiform mole).

When to Admit

- Patient cannot tolerate any food or water.
- Patient cannot ingest necessary medications.
- Weight loss.
- Presence of a hydatidiform mole.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 189: nausea and vomiting of pregnancy. Obstet Gynecol. 2018;131:e15. [Reaffirmed 2019] [PMID: 29266076]

SPONTANEOUS PREGNANCY LOSS

ESSENTIALS OF DIAGNOSIS

- Intrauterine pregnancy at less than 20 weeks' gestation.
- Low or falling levels of hCG.
- Bleeding, midline cramping pain.
- Open cervical os.
- Complete or partial expulsion of products of conception.

General Considerations

About three-fourths of spontaneous pregnancy losses (spontaneous abortions) occur before the 16th week; of these, three-fourths occur before the 8th week. Almost 20% of all clinically recognized pregnancies result in a spontaneous loss.

More than 60% of spontaneous losses result from chromosomal defects due to maternal or paternal factors; about 15% appear to be associated with maternal trauma, infections, dietary deficiencies, diabetes mellitus, hypothyroidism, antiphospholipid antibody syndrome, or anatomic malformations. There is no reliable evidence that spontaneous pregnancy loss may be induced by psychic stimuli such as severe fright, grief, anger, or anxiety. In about one-fourth of cases, the cause cannot be determined. There is no evidence that video display terminals or associated electromagnetic fields are related to an increased risk of spontaneous pregnancy loss.

It is important to distinguish women with a history of incompetent cervix from those with early pregnancy loss

which typically occur in the first trimester. Factors that predispose to incompetent cervix, a problem of the second trimester, are a history of incompetent cervix with a previous pregnancy, cervical conization or surgery, cervical injury, diethylstilbestrol (DES) exposure, and anatomic abnormalities of the cervix. Before pregnancy or during the first trimester, there are no methods for determining whether the cervix will eventually be incompetent. After 14–16 weeks, ultrasound may be used to evaluate the internal anatomy of the lower uterine segment and cervix for the funneling and shortening abnormalities consistent with cervical incompetence.

Clinical Findings

A. Symptoms and Signs

1. Incompetent cervix—Characteristically, incompetent cervix presents as "silent" cervical dilation (ie, with minimal uterine contractions) in the second trimester. When the cervix reaches 4 cm or more, active uterine contractions or rupture of the membranes may occur secondary to the degree of cervical dilation. This does not change the primary diagnosis.

2. Threatened spontaneous abortion—Bleeding or cramping occurs, but the pregnancy continues. The cervix is not dilated.

3. Inevitable spontaneous abortion—The cervix is dilated and the membranes may be ruptured, but passage of the products of conception has not yet occurred. Bleeding and cramping persist, and passage of the products of conception is considered inevitable.

4. Complete abortion—Products of conception are completely expelled. Pain ceases, but spotting may persist. Cervical os is closed.

5. Incomplete abortion—The cervix is dilated. Some portion of the products of conception remains in the uterus. Only mild cramps are reported, but bleeding is persistent and often excessive.

6. Missed abortion—The pregnancy has ceased to develop, but the conceptus has not been expelled. Missed abortion may also be referred to as early pregnancy loss. Symptoms of pregnancy disappear. There may be a brownish vaginal discharge but no active bleeding. Pain does not develop. The cervix is semifirm and slightly patulous; the uterus becomes smaller and irregularly softened; the adnexa are normal.

B. Laboratory Findings

Pregnancy tests show low or falling levels of hCG. A CBC should be obtained if bleeding is heavy. Determine Rh type and give Rh_o(D) immune globulin if Rh-negative. All tissue recovered should be assessed by a pathologist and may be sent for genetic analysis in selected cases.

C. Ultrasonographic Findings

Transvaginal ultrasound can detect the gestational sac 5–6 weeks from the last menstruation, a fetal pole at 6 weeks, and fetal cardiac activity at 6–7 weeks. Serial observations are often required to evaluate changes in size of the embryo. Diagnostic criteria of early pregnancy loss are a crown-rump length of 7 mm or more and no heartbeat or a mean sac diameter of 25 mm or more and no embryo.

Differential Diagnosis

The bleeding that occurs in abortion of a uterine pregnancy must be differentiated from the abnormal bleeding of an ectopic pregnancy and anovulatory bleeding in a nonpregnant woman. The passage of hydropic villi in the bloody discharge is diagnostic of hydatidiform mole.

Treatment

A. General Measures

1. Threatened spontaneous abortion—Studies have failed to demonstrate benefit of bedrest for 1–2 days followed by gradual resumption of usual activities. Abstinence from sexual activity has also been suggested without proven benefit. Data are lacking to support the administration of progestins to all women with a threatened abortion. If during the patient's evaluation, an infection is diagnosed (ie, UTI), it should be treated.

2. Missed abortion—This calls for counseling regarding the fate of the pregnancy and planning for its elective termination at a time chosen by the patient and clinician. Management can be medical or surgical. Each has risks and benefits. Medically induced first-trimester termination with prostaglandins (ie, misoprostol given vaginally or orally in a dose of 200–800 mcg) is safe, effective, less invasive, and more private than surgical intervention; however, if it is unsuccessful or if there is excessive bleeding, a surgical procedure (dilation and curettage) may still be needed. Patients must be counseled about the different therapeutic options.

B. Surgical Measures

1. Inevitable or incomplete spontaneous abortion—Prompt removal of any products of conception remaining within the uterus is required to stop bleeding and prevent infection. Analgesia and a paracervical block are useful, followed by uterine exploration with ovum forceps or uterine aspiration. Regional anesthesia may be required.

2. Cerclage and restriction of activities—A cerclage is the treatment of choice for incompetent cervix, but a viable intrauterine pregnancy should be confirmed before placement of the cerclage.

Cerclage should be undertaken with caution when there is advanced cervical dilation or when the membranes are prolapsed into the vagina. *Rupture of the membranes and infection are specific contraindications to cerclage.* Testing for *N gonorrhoeae, C trachomatis,* and group B streptococci should be obtained before elective placement of a cerclage. *N gonorrhoeae* and *C trachomatis* should be treated before placement.

When to Refer

- Patient with history of a second-trimester loss.
- Vaginal bleeding in a pregnant patient that resembles menstruation.

- Patient with an open cervical os.
- No signs of uterine growth in serial examinations of a pregnant patient.
- Leakage of amniotic fluid.

When to Admit

- Open cervical os.
- Heavy vaginal bleeding.
- Leakage of amniotic fluid.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 200: early pregnancy loss. Obstet Gynecol. 2018;132:e197. [PMID: 30157093]

RECURRENT PREGNANCY LOSS

According to the American Society of Reproductive Medicine, recurrent pregnancy loss is defined as the loss of two or more previable (less than 24 weeks' gestation or 500 g) pregnancies in succession. Recurrent pregnancy loss affects about 1–5% of couples. Abnormalities related to recurrent abortion can be identified in approximately 50% of these couples. If a woman has lost three previous pregnancies without identifiable cause, she still has at least a 55% chance of carrying a fetus to viability.

Recurrent pregnancy loss is a clinical rather than pathologic diagnosis. The clinical findings are similar to those observed in other types of pregnancy loss. It is appropriate to begin a medical evaluation in a woman who has had two first-trimester losses.

Treatment

A. Preconception Therapy

Preconception therapy is aimed at detection of maternal or paternal defects that may contribute to pregnancy loss. A thorough history and examination is essential. A random blood glucose test and thyroid function studies (including thyroid antibodies) can be done if history indicates a possible predisposition to diabetes mellitus or thyroid disease. Detection of lupus anticoagulant and other hemostatic abnormalities (proteins S and C and antithrombin deficiency, hyperhomocysteinemia, anticardiolipin antibody, factor V Leiden mutations) and an antinuclear antibody test may be indicated. Hysteroscopy, saline infusion sonogram, or hysterography can be used to exclude submucosal myomas and congenital anomalies of the uterus. In women with recurrent pregnancy losses, resection of a uterine septum, if present, has been recommended. Chromosomal (karyotype) analysis of both partners can be done to rule out balanced translocations (found in 3–4% of infertile couples), but karyotyping is expensive and may not be helpful.

Many therapies have been tried to prevent recurrent abortion from immunologic causes. Low-molecular-weight heparin (LMWH), aspirin, intravenous immunoglobulin, and corticosteroids have all been used but the definitive treatment has not yet been determined (see Antiphospholipid Syndrome, below). Prophylactic low-dose heparin and low-dose aspirin have been recommended for women with antiphospholipid antibodies and recurrent pregnancy loss.

B. Postconception Therapy

The patient should be provided early prenatal care and scheduled frequent office visits. Empiric sex steroid hormone therapy is complicated and should be done by an expert if undertaken.

Prognosis

The prognosis is excellent if the cause of pregnancy losses can be corrected or treated.

ECTOPIC PREGNANCY

ESSENTIALS OF DIAGNOSIS

- Amenorrhea or irregular bleeding and spotting.
- Pelvic pain, usually adnexal.
- Adnexal mass by clinical examination or ultrasound.
- Failure of serum beta-hCG to double every 48 hours.
- No intrauterine pregnancy on transvaginal ultrasound with serum beta-hCG > 2000 milli-units/mL.

General Considerations

Ectopic implantation occurs in approximately 2% of first trimester pregnancies. About 98% of ectopic pregnancies are tubal. Other sites of ectopic implantation are the peritoneum or abdominal viscera, the ovary, and the cervix. Any condition that prevents or inhibits migration of the fertilized ovum to the uterus can predispose to an ectopic pregnancy, including a history of infertility, pelvic inflammatory disease, ruptured appendix, and prior tubal surgery. Combined intrauterine and extrauterine pregnancy of two embryos (heterotopic) may occur rarely. In the United States, undiagnosed or undetected ectopic pregnancy is one of the most common causes of maternal death during the first trimester.

Clinical Findings

A. Symptoms and Signs

Severe lower quadrant pain occurs in almost every case. It is sudden in onset, stabbing, intermittent, and does not radiate. Backache may be present during attacks. Shock occurs in about 10%, often after pelvic examination. At least two-thirds of patients give a history of abnormal menstruation; many have been infertile.

Blood may leak from the tubal ampulla over a period of days, and considerable blood may accumulate in the peritoneum. Slight but persistent vaginal spotting is usually reported, and a pelvic mass may be palpated. Abdominal distention and mild paralytic ileus are often present.

B. Laboratory Findings

The CBC may show anemia and slight leukocytosis. Quantitative serum pregnancy tests will show levels generally lower than expected for normal pregnancies of the same duration. If beta-hCG levels are followed over a few days, there may be a slow rise or a plateau rather than the near doubling every 2 days associated with normal early intrauterine pregnancy or the falling levels that occur with spontaneous abortion.

C. Imaging

Ultrasonography can reliably demonstrate a gestational sac 5–6 weeks from the last menstruation and a fetal pole at 6 weeks if located in the uterus. An empty uterine cavity raises a strong suspicion of extrauterine pregnancy, which can occasionally be revealed by transvaginal ultrasound. Specified levels of serum beta-hCG have been reliably correlated with ultrasound findings of an intrauterine pregnancy; a beta-hCG level of 6500 milli-units/mL with an empty uterine cavity by transabdominal ultrasound is highly suspicious for an ectopic pregnancy. Similarly, a beta-hCG value of 2000 milli-units/mL or more can be indicative of an ectopic pregnancy if no products of conception are detected within the uterine cavity by transvaginal ultrasound. Serum beta-hCG values can vary by laboratory, so clinical decisions should not be made based solely on beta-hCG levels.

D. Special Examinations

Laparoscopy is the surgical procedure of choice both to confirm an ectopic pregnancy and in most cases to permit removal of the ectopic pregnancy without the need for exploratory laparotomy.

Ectopic pregnancy should be suspected when postabortal tissue examination fails to reveal chorionic villi. Steps must be taken for immediate diagnosis, including prompt microscopic tissue examination, ultrasonography, and serial beta-hCG titers every 48 hours.

Differential Diagnosis

Clinical and laboratory findings suggestive or diagnostic of pregnancy will distinguish ectopic pregnancy from many acute abdominal illnesses such as acute appendicitis, acute pelvic inflammatory disease, ruptured corpus luteum cyst or ovarian follicle, and urinary calculi. Uterine enlargement with clinical findings similar to those found in ectopic pregnancy is also characteristic of an aborting uterine pregnancy or hydatidiform mole.

Treatment

Patients must be warned about the complications of an ectopic pregnancy and monitored closely. In a stable patient with normal liver and renal function tests, methotrexate (50 mg/m^2) intramuscularly—given as single or multiple doses—is acceptable medical therapy for early ectopic pregnancy. Favorable criteria are that the pregnancy should be less than 3.5 cm in largest dimension and unruptured, with no active bleeding and no fetal heart tones. Several small studies have not found an increased risk of fetal malformations or pregnancy losses in women who conceive within 6 months of methotrexate therapy.

When a patient with an ectopic pregnancy is unstable or when surgical therapy is planned, the patient is hospitalized. Blood is typed and cross-matched. The goal is to diagnose and operate before there is frank rupture of the tube and intra-abdominal hemorrhage. *The use of methotrexate in an unstable patient is absolutely contraindicated.*

Surgical treatment is definitive. In most patients, diagnostic laparoscopy is the initial surgical procedure performed. Depending on the size of the ectopic pregnancy and whether or not it has ruptured, salpingostomy with removal of the ectopic pregnancy or a partial or complete salpingectomy can usually be performed. Clinical conditions permitting, patency of the contralateral tube can be established by injection of indigo carmine into the uterine cavity and flow through the contralateral tube confirmed visually by the surgeon; iron therapy for anemia may be necessary during convalescence. Rh_o(D) immune globulin (300 mcg) should be given to Rh-negative patients.

Prognosis

Repeat tubal pregnancy occurs in about 10% of cases. This should not be regarded as a contraindication to future pregnancy, but the patient requires careful observation and early ultrasound confirmation of an intrauterine pregnancy.

When to Refer

- Severe abdominal pain.
- Palpation of an adnexal mass on pelvic examination.
- Abdominal pain and vaginal bleeding in a pregnant patient.

When to Admit

Presence of symptoms or signs of a ruptured ectopic pregnancy.

Carusi D. Pregnancy of unknown location: evaluation and management. Semin Perinatol. 2019;43:95. [PMID: 30606496]

GESTATIONAL TROPHOBLASTIC DISEASE (Hydatidiform Mole & Choriocarcinoma)

ESSENTIALS OF DIAGNOSIS

Hydatidiform mole

- Amenorrhea.
- Irregular uterine bleeding.
- Serum beta-hCG > 40,000 milli-units/mL.
- Passage of grapelike clusters of enlarged edematous villi per vagina.

- Uterine ultrasound shows characteristic heterogeneous echogenic image and no fetus or placenta.
- Cytogenetic composition is 46,XX (85%), of paternal origin.

Choriocarcinoma

- Persistence of detectable beta-hCG after mole evacuation.

General Considerations

Gestational trophoblastic disease is a spectrum of disorders that includes hydatidiform mole (partial and complete), invasive mole (local extension into the uterus or vagina), choriocarcinoma (malignancy often complicated by distant metastases), and placental site trophoblastic tumor. Complete moles show no evidence of a fetus on ultrasonography. The majority are 46,XX, with all chromosomes of paternal origin. Partial moles generally show evidence of an embryo or gestational sac; are triploid, slower-growing, and less symptomatic; and often present clinically as a missed abortion. Partial moles tend to follow a benign course, while complete moles have a greater tendency to become choriocarcinoma.

In North America, the frequency of gestational trophoblastic disease is 1:1500 pregnancies. The highest rates occur in Asian persons. Risk factors include prior spontaneous abortion, a history of mole, and age younger than 21 or older than 35. Approximately 10% of women require further treatment after evacuation of the mole; choriocarcinoma develops in 2–3% of women.

Clinical Findings

A. Symptoms and Signs

Uterine bleeding, beginning at 6–16 weeks, is observed in most instances. In some cases, the uterus is larger than would be expected in a normal pregnancy of the same duration. Excessive nausea and vomiting may occur. Bilaterally enlarged cystic ovaries are sometimes palpable. They result from ovarian hyperstimulation due to excess beta-hCG.

Preeclampsia-eclampsia may develop during the second trimester of an untreated molar pregnancy, but this is unusual because most are diagnosed early.

Choriocarcinoma may be manifested by continued or recurrent uterine bleeding after evacuation of a mole or following delivery, abortion, or ectopic pregnancy. An ulcerative vaginal tumor, pelvic mass, or distant metastases may be the presenting manifestation.

B. Laboratory Findings

Hydatidiform moles are generally characterized by high serum beta-hCG values, which can range from high normal to the millions. Levels are higher with complete moles than with partial moles. Serum beta-hCG values, if extremely high, can assist in making the diagnosis, but they are more helpful in managing response to treatment. Hemoglobin/hematocrit, creatinine, blood type, liver biochemical tests, and thyroid function tests should also be measured. High beta-hCG levels can cause the release of thyroid hormone, and rarely, symptoms of hyperthyroidism. Patients with hyperthyroidism may require beta-blocker therapy until the mole has been evacuated.

C. Imaging

The preoperative diagnosis of hydatidiform mole is confirmed by ultrasound. Placental vesicles can be easily seen on transvaginal ultrasound. A preoperative chest film is indicated to rule out pulmonary metastases of the trophoblast.

Treatment

A. Specific (Surgical) Measures

The uterus should be emptied as soon as the diagnosis of hydatidiform mole is established, preferably by suction curettage. The products of conception removed from the uterus should be sent to a pathologist for review. Ovarian cysts should not be resected nor ovaries removed; spontaneous regression of theca lutein cysts will occur with elimination of the mole. In patients who have completed their childbearing, hysterectomy is an acceptable alternative. Hysterectomy does not preclude the need for follow-up of beta-hCG levels.

B. Follow-Up Measures

Weekly quantitative beta-hCG level measurements are initially required. Following successful surgical evacuation, moles show a progressive decline in beta-hCG. After three negative weekly tests (less than 5 milli-units/mL), the interval may be increased to every 1 month for an additional 6 months. The purpose of this follow-up is to identify persistent nonmetastatic and metastatic disease, including choriocarcinoma, which is more likely to occur if the initial beta-hCG is high and the uterus is large. If levels plateau or begin to rise, the patient should be evaluated by repeat laboratory tests, chest film, and dilatation and curettage (D&C) before the initiation of chemotherapy. Effective contraception (preferably birth control pills) should be prescribed to avoid the hazard and confusion of elevated beta-hCG from a new pregnancy. The beta-hCG levels should be negative for 6 months before pregnancy is attempted again. Because the risk of recurrence of a molar pregnancy is 1–2%, an ultrasound should be performed in the first trimester of the pregnancy following a mole to ensure that the pregnancy is normal. In addition, a beta-hCG level should then be checked 6 weeks postpartum (after the subsequent normal pregnancy) to ensure there is no persistent trophoblastic tissue, and the placenta should be examined by a pathologist.

C. Antitumor Chemotherapy

If malignant tissue is discovered at surgery or during the follow-up examination, chemotherapy is indicated. For low-risk patients with a good prognosis, methotrexate is considered first-line therapy followed by dactinomycin (see Table 39–3). Patients with high-risk disease should be referred to a cancer center, where multiple-agent chemotherapy probably will be given.

Prognosis

Five-year survival after courses of chemotherapy, even when metastases have been demonstrated, can be expected in at least 85% of cases of choriocarcinoma.

When to Refer

- Uterine size exceeds that anticipated for gestational age.
- Vaginal bleeding similar to menstruation.
- Pregnant patient with a history of a molar pregnancy.

When to Admit

- Confirmed molar pregnancy by ultrasound and laboratory studies.
- Heavy vaginal bleeding in a pregnant patient under evaluation.

Elias KM et al. State-of-the-art workup and initial management of newly diagnosed molar pregnancy and postmolar gestational trophoblastic neoplasia. J Natl Compr Canc Netw. 2019;17:1396. [PMID: 31693988]

OBSTETRICAL COMPLICATIONS OF THE SECOND & THIRD TRIMESTERS

PREECLAMPSIA-ECLAMPSIA

ESSENTIALS OF DIAGNOSIS

Gestational hypertension

- Blood pressure of ≥ 140/90 mm Hg systolic or > 90 mm Hg diastolic after 20 weeks' gestation.

Preeclampsia

- Blood pressure of ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic after 20 weeks' gestation.
- Proteinuria of ≥ 0.3 g in 24 hours.

Preeclampsia with severe features

- Blood pressure of ≥ 160 mm Hg systolic or ≥ 110 mm Hg diastolic.
- Progressive kidney injury.
- Thrombocytopenia.
- Hemolysis, elevated liver enzymes, low platelets (HELLP).
- Pulmonary edema.
- Vision changes or headache.
- When hypertension is present with severe features of preeclampsia, seizure prophylaxis could be beneficial.

Eclampsia

- Seizures in a patient with evidence of preeclampsia.

General Considerations

Preeclampsia is defined as the presence of newly elevated blood pressure and proteinuria during pregnancy. Eclampsia is diagnosed when seizures develop in a patient with evidence of preeclampsia. Historically, three elements were required for the diagnosis of preeclampsia: hypertension, proteinuria, and edema. Edema was difficult to objectively quantify and is no longer a required element. In addition, proteinuria may not always be present in preeclampsia with severe features.

Preeclampsia-eclampsia most commonly occurs in the third trimester but can occur any time after 20 weeks' gestation and up to 6 weeks postpartum.

Risk factors for early preeclampsia-eclampsia are maternal comorbid conditions, such as hypertension, kidney disease, and SLE.

Preeclampsia-eclampsia is a disease unique to pregnancy, with the only cure being delivery of the fetus and placenta. Preeclampsia develops in approximately 7% of pregnant women in the United States; of those, eclampsia will develop in 5% (0.04% of pregnant women). Primiparas are most frequently affected; however, the incidence of preeclampsia-eclampsia is increased with multifetal gestations, preeclampsia in a previous pregnancy, and comorbid diseases such as chronic hypertension, pregestational diabetes, gestational diabetes, thrombophilia, kidney disease, SLE, prepregnancy BMI above 30, antiphospholipid antibody syndrome, maternal age 35 years or older, assisted reproductive technology, and obstructive sleep apnea. Eclampsia is a significant cause of maternal death.

Clinical Findings

The severity of preeclampsia-eclampsia is based on its effect on six major target areas: the CNS, the kidneys, the liver, the hematologic system, the vascular system, and the fetal-placental unit. By evaluating each of these areas for the presence of mild to severe preeclampsia, the degree of involvement can be assessed, and an appropriate management plan can be formulated that balances the severity of disease and gestational age (Table 19–3).

A. Preeclampsia

1. Without severe features—Patients usually have few complaints, and the diastolic blood pressure is less than 110 mm Hg. Edema may be present. The platelet count is over 100,000/mcL (100×10^9/L), antepartum fetal testing is reassuring, CNS irritability is minimal, epigastric pain is not present, and liver enzymes are not elevated. Proteinuria is present with urine protein greater than or equal to 0.3/24 hours. Gestational hypertension may be present in the absence of proteinuria.

2. With severe features—Symptoms are more dramatic and persistent. Patients may complain of headache and changes in vision. The blood pressure is often above 160/110 mm Hg. Thrombocytopenia (platelet count less than 100,000/mcL [100×10^9/L]) may be present and progress to disseminated intravascular coagulation. Severe epigastric pain may be present from hepatic subcapsular

Table 19–3. Indicators of mild and severe preeclampsia-eclampsia and gestational hypertension with severe features.

Site	Indicator	Mild	Severe
CNS	Symptoms and signs	Hyperreflexia	Seizures, blurred vision, scotomas, headache, clonus, irritability
Kidney	Proteinuria Urinary output	> 0.3 g/24 hours > 30 mL/hour	> 0.3 g/24 hours < 30 mL/hour
Liver	AST, ALT, LD	Normal liver enzymes	Elevated liver enzymes, epigastric pain, ruptured liver
Hematologic	Platelets Hemoglobin	Normal Normal	< 100,000/mcL (100×10^9/L) Low, normal, or elevated
Vascular	Blood pressure Retina	< 160/110 mm Hg Arteriolar spasm	> 160/110 mm Hg Retinal hemorrhages
Fetal-placental unit	Growth restriction Oligohydramnios Fetal distress	Absent Absent Absent	Present Present Present

hemorrhage with significant stretch or rupture of the liver capsule. HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) is an advanced form of severe preeclampsia.

B. Eclampsia

The occurrence of seizures defines eclampsia. It is a manifestation of severe CNS involvement. Other findings of preeclampsia are observed.

Differential Diagnosis

Other diseases that can mimic preeclampsia-eclampsia include chronic hypertension, CKD, primary seizure disorders, gallbladder and pancreatic disease, immune thrombocytopenia, thrombotic thrombocytopenic purpura, and hemolytic-uremic syndrome.

Treatment

The American College of Obstetricians and Gynecologists (ACOG) supports considering the use of low-dose aspirin (81 mg orally daily) initiated between 12 weeks' and 28 weeks' gestation for women at increased risk for preeclampsia; risk factors include a history of preeclampsia, multifetal gestation, chronic hypertension, diabetes mellitus, kidney disease, or autoimmune diseases (such as SLE or antiphospholipid syndrome). Clinicians may also consider low-dose aspirin (81 mg orally daily) if more than one of the following moderate risk factors are present: nulliparity, obesity, family history of preeclampsia, Black race, age greater than 35 years, low socioeconomic status, and personal history factors (eg, mother having a previous baby with low birth weight). In clinical studies, diuretics, dietary restriction or enhancement, sodium restriction, and vitamin-mineral supplements (eg, calcium or vitamin C and E) have not been confirmed to be useful. The only cure is delivery of the fetus at a time as favorable as possible for its survival.

A. Preeclampsia

Early recognition is the key to treatment. This requires careful attention to the details of prenatal care—especially subtle changes in blood pressure and weight. The objectives are to prolong pregnancy, if possible, to allow fetal lung maturity while preventing progression to severe disease and eclampsia. The critical factors are the gestational age of the fetus, fetal pulmonary maturity, and the severity of maternal disease. Preeclampsia-eclampsia without severe features and gestational hypertension at term is managed by delivery. Before term, severe preeclampsia-eclampsia requires delivery with very few exceptions. Epigastric pain, seizures, severe range blood pressures, thrombocytopenia, and visual disturbances are strong indications for delivery of the fetus. Marked proteinuria alone can be managed more conservatively.

1. Home management—Home management may be attempted for patients with gestational hypertension and preeclampsia without severe features and a stable home situation. This requires assistance at home, rapid access to the hospital, a reliable patient, and the ability to obtain frequent blood pressure readings. A home health nurse can often provide frequent home visits and assessments.

2. Hospital care—Hospitalization is required for women with preeclampsia with severe features or those with unpredictable home situations. Regular assessments of blood pressure, urine protein, and fetal heart tones and activity are required. A CBC with platelet count, electrolyte panel, and liver enzymes should be checked regularly, with frequency dependent on severity. A 24-hour urine collection for total protein and creatinine clearance should be obtained on admission and repeated as indicated. Magnesium sulfate is not used until the diagnosis of severe preeclampsia is made and delivery planned (see Eclampsia, below).

Fetal evaluation should be obtained as part of the workup. If the patient is being admitted to the hospital, fetal testing should be performed on the same day to assess fetal well-being. This may be done by fetal heart rate testing with nonstress testing or by biophysical profile. A regular schedule of fetal surveillance must then be followed. Daily fetal kick counts can be recorded by the patient herself. If the fetus is less than 34 weeks' gestation, corticosteroids (betamethasone 12 mg intramuscularly every 24 hours for

two doses, or dexamethasone 6 mg intramuscularly every 12 hours for four doses) can be administered to the mother. *However, when a woman clearly has unstable severe preeclampsia, delivery should not be delayed for fetal lung maturation or administration of corticosteroids.* In women with gestational hypertension or preeclampsia without severe features at or beyond 37 weeks' gestation, delivery rather than expectant management (eg, watchful waiting or close monitoring) upon diagnosis is recommended.

The method of delivery is determined by the maternal and fetal status. A vaginal delivery is preferred because it has less blood loss than a cesarean section and requires less coagulation factors. Cesarean section is reserved for the usual fetal indications. For mild preeclampsia, delivery should take place at term.

B. Eclampsia

1. Emergency care—If the patient is convulsing, she is turned on her side to prevent aspiration and to improve blood flow to the placenta. The seizure may be stopped by giving an intravenous bolus of magnesium sulfate (the preferred agent), 4–6 g over 4 minutes or until the seizure stops. A continuous intravenous infusion of magnesium sulfate is then started at a rate of 2–3 g/hour unless the patient has reduced kidney function (serum creatinine 1.0–1.5 mg/dL). Reducing maintenance dosing to 1 g/hour or temporarily stopping infusion may be necessary to address instances of kidney dysfunction and magnesium toxicity. Magnesium blood levels may be checked every 4–6 hours and ideally the infusion rate adjusted to maintain a therapeutic blood level (4–7 mEq/L). Urinary output is checked hourly, and the patient assessed for signs of possible magnesium toxicity such as loss of deep tendon reflexes or decrease in respiratory rate and depth, which can be reversed with calcium gluconate, 1 g intravenously over 2 minutes. If seizures continue, an additional dose of magnesium sulfate, 2 g intravenously, may be infused. Alternative agents should be used only if magnesium sulfate is unavailable.

2. General care—In patients who have preeclampsia with severe features, magnesium sulfate should be given intravenously, 4- to 6-g load over 15–20 minutes followed by 2–3 g/hour maintenance, for seizure prophylaxis. Eclampsia necessitates delivery once the patient is stabilized. It is important, however, that assessment of the status of the patient and fetus take place first. Continuous fetal monitoring must be performed and maternal blood typed and cross-matched quickly. A urinary catheter is inserted to monitor urinary output, and a CBC with platelets, electrolytes, creatinine, and liver enzymes are obtained. If hypertension is present with systolic values of 160 mm Hg or higher or diastolic values 110 mm Hg or higher, antihypertensive medications should be administered to reduce the blood pressure to 140–150/90–100 mm Hg. Lower blood pressures than this may induce placental insufficiency through reduced perfusion. Hydralazine, given in 5- to 10-mg increments intravenously every 20 minutes, is frequently used to lower blood pressure. Labetalol, 10–20 mg intravenously, every 20 minutes as needed, can also be used. Immediate-release oral nifedipine 10–20 mg may be administered and then repeated in 20 minutes, followed by 10–20 mg every 4–6 hours for a maximum daily dosage of 180 mg. This medication is helpful if the patient does not have intravenous access.

3. Delivery—Delivery is mandated once eclampsia has occurred. Vaginal delivery is preferred. Subsequent prolonged fetal heart rate decelerations are frequent after an eclamptic seizure. However, delivery should proceed only after there is maternal hemodynamic stabilization. Furthermore, maternal resuscitation is usually followed by normalization of the fetal tracing. The rapidity with which delivery must be achieved depends on the fetal and maternal status following the seizure and the availability of laboratory data on the patient. Oxytocin, given intravenously and titrated to a dose that results in adequate contractions, may be used to induce or augment labor. Oxytocin should only be administered by a clinician specifically trained in its use. Regional analgesia or general anesthesia is acceptable. Cesarean section is used for the usual obstetric indications.

4. Postpartum—Magnesium sulfate infusion (2–3 g/hour with noted exceptions, see above) should be continued for 24 hours postpartum. Late-onset preeclampsia-eclampsia can occur during the postpartum period. It is usually manifested by either hypertension or seizures. Treatment is the same as before delivery—ie, with hydralazine and magnesium sulfate.

When to Refer

- New onset of hypertension and proteinuria in a pregnant patient more than 20 weeks' gestation.
- New onset of seizure activity in a pregnant patient.

When to Admit

- Symptoms of preeclampsia with severe features in a pregnant patient with elevated blood pressure above baseline.
- Evaluation for preeclampsia when severe features of the disease are suspected.
- Evaluation for preeclampsia in a patient with an unstable home environment.
- Evidence of eclampsia.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 222: gestational hypertension and preeclampsia. Obstet Gynecol. 2020;135:e237. [PMID: 32443079]

PRETERM LABOR

ESSENTIALS OF DIAGNOSIS

- Preterm regular uterine contractions approximately 5 minutes apart.
- Cervical dilatation, effacement, or both.

General Considerations

Preterm birth is defined as birth between 20 0/7 and 36 6/7 weeks' gestation, and spontaneous preterm labor with or without premature rupture of the fetal membranes causes at least two-thirds of all preterm births. Prematurity is the largest single contributor to infant mortality, and survivors are at risk for a myriad of short- and long-term complications. It also the most common reason for antepartum hospitalization. Rates of infant death and long-term neurologic impairment are inversely related to gestational age at birth. The cusp of viability in contemporary practice is 23–25 weeks' gestation, and infants born before 23 weeks rarely survive. About two-thirds of the preterm births occur between 34 weeks and 36 weeks and 6 days (termed "late preterm birth"), and good outcomes are expected at these gestational ages. Importantly, however, even these late preterm infants are at significantly increased risk for both morbidity and mortality when compared to those infants born at term.

Major risk factors for spontaneous preterm labor include a past history of preterm birth and a short cervical length as measured by transvaginal ultrasound. Other known risk factors include Black race, multifetal pregnancies, intrauterine infection, substance abuse, smoking, periodontal disease, and socioeconomic deprivation. Numerous preterm births are preceded by ruptured membranes.

Clinical Findings

In women with regular uterine contractions and cervical change, the diagnosis of preterm labor is straightforward. However, symptoms such as pelvic pressure, cramping, or vaginal discharge may be the first complaints in high-risk patients who later develop preterm labor. Because these complaints may be vague and irregular uterine contractions are common, distinguishing which patients merit further evaluation can be problematic. In some cases, this distinction can be facilitated by the use of fetal fibronectin measurement in cervicovaginal specimens. This test is most useful when it is negative (less than 50 ng/mL), since the negative predictive value for delivery within 7–14 days is 93–97%. A negative test, therefore, usually means the patient can be reassured and discharged home. Because of its low sensitivity, however, fetal fibronectin is not recommended as a screening test in asymptomatic women.

Treatment

A. General Measures

Patients must be educated to identify symptoms associated with preterm labor to avoid unnecessary delay in their evaluation. In patients who are believed to be at increased risk for preterm delivery, randomized trials have failed to demonstrate improved outcomes in women placed on activity restriction. Paradoxically, such recommendations may place a woman at an *increased* risk to deliver preterm. Women with preterm labor at the threshold of viability present unique ethical and obstetric challenges and are best managed in consultation with maternal-fetal medicine and neonatology specialists. The families in such situations should be actively and continually engaged about decisions regarding the aggressiveness of resuscitative efforts.

B. Corticosteroids

In pregnancies between 23 weeks' and 34 weeks' gestation where preterm birth is anticipated, a single short course of corticosteroids should be administered to promote fetal lung maturity. Such therapy has been demonstrated to reduce the frequency of respiratory distress syndrome, intracranial hemorrhage, and even death in preterm infants. Betamethasone, 12 mg intramuscularly repeated once 24 hours later, and dexamethasone, 6 mg intramuscularly repeated every 12 hours for four doses, both cross the placenta and are the preferred treatments in this setting. A single repeat course of antenatal corticosteroids should be considered in women who are at risk for preterm delivery within the next 7 days, and whose prior dose of antenatal corticosteroids was administered more than 14 days previously. Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario. Administration of betamethasone may be considered in pregnant women between 34 0/7 and 36 6/7 weeks' gestation at imminent risk for preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.

C. Antibiotics

Despite the finding that preterm labor is associated with intrauterine infection in certain cases, there is no evidence that antibiotics forestall delivery in women with preterm labor and intact membranes. However, women in preterm labor should receive antimicrobial prophylaxis against group B *streptococcus* unless a single standard culture of the distal vagina and anorectum has been negative for the organism in the preceding 5 weeks. Notably, there is usually not enough time in this clinical setting to culture and test isolates. The recommended regimen for antimicrobial prophylaxis against group B *Streptococcus* is penicillin G, 5 million units intravenously as a loading dose and then 2.5–3 million units intravenously every 4 hours until delivery. In penicillin-allergic patients not at high risk for anaphylaxis, 2 g of cefazolin can be given intravenously as an initial dose and then 1 g intravenously every 8 hours until delivery. In patients at high risk for anaphylaxis, vancomycin, 20 mg/kg intravenously every 8 hours until delivery, can be used. Clindamycin, 900 mg intravenously every 8 hours until delivery, can also be used after a group B streptococcal isolate has been confirmed to be susceptible to clindamycin.

D. Tocolytic Agents

Evidence supports the use of first-line tocolytic treatment to forestall delivery with beta-adrenergic receptor agonists, calcium channel blockers, or indomethacin for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal corticosteroids, and (if appropriate), transport the patient to a facility better equipped to care for premature infants. Maintenance

therapy (continuation of treatment beyond 48 hours) is not effective at preventing preterm birth and is not recommended.

Beta-adrenergic drugs, such as terbutaline, can be given every 30 minutes as an intravenous infusion starting at 2.5 mcg/minute or as a subcutaneous injection starting at 250 mcg. Oral terbutaline is not recommended because of the lack of proven efficacy and concerns about maternal safety. Serious maternal side effects have been reported with the use of terbutaline and include tachycardia, pulmonary edema, arrhythmias, metabolic derangements (such as hyperglycemia and hypokalemia), and even death. Pulmonary edema occurs with increased frequency with concomitant administration of corticosteroids, large-volume intravenous fluid infusion, maternal sepsis, or prolonged tocolysis. Because of these safety concerns, the US FDA warns that terbutaline be administered exclusively in a hospital setting and discontinued after 48–72 hours of treatment.

Nifedipine, 20 mg orally every 6 hours, and **indomethacin**, 50 mg orally once then 25 mg orally every 6 hours up to 48 hours, have been used with limited success.

Magnesium sulfate is commonly used (but no longer recommended as a first-line agent) for tocolysis, and there is evidence that it may also be protective against cerebral palsy in infants from 24 weeks' to 32 weeks' gestation when given at time of birth. Magnesium sulfate is given intravenously as a 4- to 6-g bolus followed by a continuous infusion of 2 g/hour. Magnesium levels are not typically checked but should be monitored if there is any concern for toxicity. Magnesium sulfate is entirely cleared by the kidney and must, therefore, be used with caution in women with any degree of kidney disease.

Before attempts are made to prevent preterm delivery with tocolytic agents, the patient should be assessed for conditions in which delivery would be indicated. Severe preeclampsia, lethal fetal anomalies, placental abruption, and intrauterine infection are all examples of indications for preterm delivery. In such cases, attempts to forestall delivery would be inappropriate.

Preterm Birth Prevention

Strategies aimed at preventing preterm birth in high-risk women—principally those with a history of preterm birth or a shortened cervix (or both)—have focused on the administration of progesterone or progesterone compounds and the use of cervical cerclage. Prospective randomized controlled trials have demonstrated reductions in rates of preterm birth in high-risk women with singleton pregnancies who received progesterone supplementation, although the optimal preparation, dose, and route of administration (intramuscular injection versus vaginal suppository) are unclear. Although the issue has not been settled, there is some evidence that progesterone therapy may decrease rates of preterm birth in nulliparous women who have a shortened cervix as measured by transvaginal ultrasound. The ACOG does not recommend universal transvaginal cervical length screening but acknowledges that this strategy may be considered.

There is also evidence that women with a previous spontaneous preterm birth and a shortened cervix (less than 25 mm before 24 weeks' gestation) may benefit from placement of a cervical cerclage. Incidentally detected short cervical length in the second trimester in the absence of a prior singleton preterm birth is not diagnostic of cervical insufficiency, and cerclage is not indicated in this setting. In twin and triplet gestations, however, neither progesterone administration nor cervical cerclage placement has been effective at prolonging pregnancy, and these therapies are not recommended in women with multifetal pregnancies.

When to Refer

- Symptoms of increased pelvic pressure or cramping in high-risk patients.
- Regular uterine contractions.
- Rupture of membranes.
- Vaginal bleeding.

When to Admit

- Cervical dilation of 2 cm or more before 34 weeks' gestation.
- Contractions that cause cervical change.
- Rupture of membranes.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin, No 234: prediction and prevention of spontaneous preterm birth. Obstet Gynecol. 2021;138:945. [PMID: 34794160]

American College of Obstetricians and Gynecologists. Practice Advisory: use of antenatal corticosteroids at 22 weeks of gestation. 2021 Sep. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/09/use-of-antenatal-corticosteroids-at-22-weeks-of-gestation

American College of Obstetricians and Gynecologists. Practice Bulletin No. 217: prelabor rupture of membranes. Obstet Gynecol. 2020;135:e80. [PMID: 32080050]

THIRD-TRIMESTER BLEEDING

Five to 10 percent of women have vaginal bleeding in late pregnancy. The clinician must distinguish between placental causes (placenta previa, placental abruption, vasa previa) and nonplacental causes (labor, infection, disorders of the lower genital tract, systemic disease. The approach to bleeding in late pregnancy depends on the underlying cause, the gestational age at presentation, the degree of blood loss, and the overall status of the mother and her fetus. The cause of antepartum bleeding after mid-pregnancy is unknown in one-third of cases.

Treatment

A. General Measures

The patient should initially be observed closely with continuous fetal monitoring to assess for fetal distress. A CBC with platelets and a prothrombin time (INR) should be obtained and repeated serially if the bleeding continues. If hemorrhage is significant or if there is evidence of acute hypovolemia, the need for transfusion should be anticipated and an appropriate volume of red cells prepared with

cross-matching. Ultrasound examination should be performed to determine placental location. Digital pelvic examinations are done only after ultrasound examination has ruled out placenta previa. Administration of anti-D immune globulin may be required for women who are Rh negative.

B. Placenta Previa

Placenta previa occurs when the placenta implants over the internal cervical os. Risk factors for this condition include previous cesarean delivery, increasing maternal age, multiparity, and cigarette smoking. If the diagnosis is initially made in the first or second trimester, the ultrasound should be repeated in the third trimester. Persistence of placenta previa at this point is an indication for cesarean as the route of delivery. Painless vaginal bleeding is the characteristic symptom in placenta previa and can range from light spotting to profuse hemorrhage. Hospitalization for extended evaluation is the appropriate initial management approach. For pregnancies that have reached 37 weeks' gestation or beyond with continued bleeding, cesarean delivery is generally indicated. Pregnancies at 36 weeks or earlier are candidates for expectant management provided the bleeding is not prodigious, and a subset of these women can be discharged if the bleeding and contractions completely subside.

C. Morbidly Adherent Placenta

Morbidly adherent placenta is a general term describing an abnormally adherent placenta that has invaded into the uterus. The condition can be further classified depending on whether the depth of invasion is limited to the endometrium (*accreta*), extends into the myometrium (*increta*), or invades beyond the uterine serosa (*percreta*). The most important risk factor for a morbidly adherent placenta is a prior uterine scar—typically from one or more prior cesarean deliveries. The focus of invasion usually involves the scar itself, and *placenta previa* is commonly associated with morbid adherence. Obstetric care providers are concerned with the incidence of these syndromes has increased dramatically over the last 50 years commensurate with the increasing cesarean delivery rate.

After delivery of the infant, almost always in a repeat cesarean section, the morbidly adherent placenta does not separate normally, and the bleeding that results can be torrential. Emergency hysterectomy is usually required to stop the hemorrhage, and transfusion requirements are often massive. Because of the considerable increase in both maternal morbidity and mortality associated with this condition, careful preoperative planning is imperative when the diagnosis is suspected antenatally. Ultrasound findings such as intraplacental lacunae, bridging vessels into the bladder, and loss of the retroplacental clear space suggest placental invasion in women who have placenta previa. *Importantly, however, even if ultrasound findings are subtle, an abnormally adherent placenta should be suspected in any patient with one or more prior cesarean deliveries and an anterior placenta previa*. Ideally, delivery planning should involve a multidisciplinary team, and the surgery should take place at an institution with appropriate personnel and a blood bank equipped to handle patients requiring massive transfusion. It has been demonstrated that a systematic approach to management with a multidisciplinary team improves patient outcomes. Evidence-based recommendations regarding delivery timing are lacking, but the goal is to have a planned, late-preterm cesarean delivery. As such, delivery at 34–36 weeks in a stable patient seems a reasonable approach.

D. Placental Abruption

Placental abruption is the premature separation of the placenta from its implantation site before delivery. Risk factors for abruption include hypertension, multiparity, cocaine use, cigarette smoking, previous abruption, and thrombophilias. Classic symptoms are vaginal bleeding, uterine tenderness, and frequent contractions, but the clinical presentation is highly variable. There is often concealed hemorrhage when the placenta abrupts, which causes increased pressure in the intervillous space. Excess amounts of thromboplastin escape into the maternal circulation and defibrination occurs. Profound coagulopathy and acute hypovolemia from blood loss can occur and are more likely with an abruption severe enough to kill the fetus. Ultrasound may be helpful to exclude placenta previa, but failure to identify a retroplacental clot does not exclude abruption. In most cases, abruption is an indication for immediate cesarean delivery because of the high risk of fetal death.

American College of Obstetricians and Gynecologists. Obstetric Care Consensus No. 7: placenta accreta spectrum. Obstet Gynecol. 2018;132:e259. [PMID: 30461695]

American College of Obstetricians and Gynecologists. Practice Bulletin No. 183: postpartum hemorrhage. Obstet Gynecol. 2017;130:e168. [Reaffirmed 2019] [PMID: 28937571]

OBSTETRIC COMPLICATIONS OF THE PERIPARTUM PERIOD

PUERPERAL MASTITIS

Postpartum mastitis occurs sporadically in nursing mothers, usually with symptom onset after discharge from the hospital. *Staphylococcus aureus* is usually the causative agent. Women nursing for the first time and those with difficulty breastfeeding appear to be at greatest risk. Rarely, inflammatory carcinoma of the breast can be mistaken for puerperal mastitis (see also Chapter 17). Unfortunately, strategies aimed at preventing mastitis in breastfeeding women have been unsuccessful.

Mastitis frequently begins within 3 months after delivery and may start with an engorged breast and a sore or fissured nipple. Cellulitis is typically unilateral with the affected area of breast being red, tender, and warm. Fever and chills are common complaints as well. Treatment consists of antibiotics effective against penicillin-resistant staphylococci (dicloxacillin 500 mg orally every 6 hours or a cephalosporin for 10–14 days) and regular emptying of the breast by nursing or by using a mechanical suction

device. Although nursing from the infected breast is safe for the infant, local inflammation of the nipple may complicate latching. Failure to respond to usual antibiotics within 3 days may represent an organizing abscess or infection with a resistant organism. The risk for abscess formation is increased when the causative organism is methicillin-resistant *S aureus* (MRSA), compared with infection from nonresistant staphylococcal species. If an abscess is suspected, ultrasound of the breast can help confirm the diagnosis. In these cases, aspiration or surgical evacuation is usually required. Changing antibiotics based on culture sensitivity (to vancomycin or trimethoprim-sulfamethoxazole, for example) is useful, especially if the clinical course is not improving appropriately.

CHORIOAMNIONITIS & METRITIS

ESSENTIALS OF DIAGNOSIS

- Fever not attributable to another source.
- Uterine tenderness.
- Tachycardia in the mother, fetus, or both.

General Considerations

Pelvic infections are relatively common problems encountered during the peripartum period. Chorioamnionitis is an infection of the amnion and chorion (fetal parts), usually occurring during labor. Uterine infection after delivery is often called endometritis or endomyometritis, but the term "metritis" is probably most accurate to emphasize that the infection extends throughout the uterine tissue. These infections are polymicrobial and are most commonly attributed to urogenital pathogens. The single most important risk factor for puerperal infection is cesarean delivery, which increases the risk from 5- to 20-fold. Other recognized risk factors include prolonged labor, use of internal monitors, nulliparity, multiple pelvic examinations, prolonged rupture of membranes, and lower genital tract infections. Although maternal complications such as dysfunctional labor and postpartum hemorrhage are increased with clinical chorioamnionitis, the principal reason to initiate treatment is to prevent morbidity in the offspring. Neonatal complications such as sepsis, pneumonia, intraventricular hemorrhage, and cerebral palsy are increased in the setting of chorioamnionitis. Intrapartum initiation of antibiotics, however, significantly reduces neonatal morbidity.

Clinical Findings

Puerperal infections are diagnosed principally by the presence of fever (38°C or higher) in the absence of any other source and one or more of the following signs: maternal or fetal tachycardia (or both), and uterine tenderness. Foul-smelling lochia may be present but is an insensitive marker of infection as many women without infection may experience an unpleasant odor. Likewise, some life-threatening infections such as necrotizing fasciitis are typically odorless. Cultures are typically not done because of the polymicrobial nature of the infection.

Treatment

Treatment is empiric with broad-spectrum antibiotics that will cover gram-positive and gram-negative organisms if still pregnant and gram-negative organisms and anaerobes if postpartum. A common regimen for chorioamnionitis is ampicillin, 2 g intravenously every 6 hours, and gentamicin, 2 mg/kg intravenous load then 1.5 mg/kg intravenously every 8 hours. A common regimen for metritis is gentamicin, 2 mg/kg intravenous load then 1.5 mg/kg intravenously every 8 hours, and clindamycin, 900 mg intravenously every 8 hours. Antibiotics are stopped in the mother when she has been afebrile and asymptomatic for 24 hours. No oral antibiotics are subsequently needed. Patients with metritis who do not respond in the first 24–48 hours may have an enterococcal component of metritis and require additional gram-positive coverage (such as ampicillin) to the regimen.

MEDICAL CONDITIONS COMPLICATING PREGNANCY

ANEMIA

Normal pregnancy is characterized by an increase in maternal plasma volume of about 50% and an increase in red cell volume of about 25%. Because of these changes, the mean hemoglobin and hematocrit values are lower than in the nonpregnant state. Anemia in pregnancy is considered when the hemoglobin measurement is below 11 g/dL in the first trimester, 10.5 g/dL in the second trimester, and 11 g/dL in the third trimester. By far, the most common causes are iron deficiency and acute blood loss anemia, the latter usually occurring in the peripartum period. Symptoms such as fatigue and dyspnea that would otherwise suggest the presence of anemia in nonpregnant women are common in pregnant women; therefore, periodic measurement of hematocrits in pregnancy is essential so that anemia can be identified and treated. In addition to its impact on maternal health, untoward pregnancy outcomes such as low birthweight and preterm delivery have been associated with second- and third-trimester anemia.

A. Iron Deficiency Anemia

The increased requirement for iron over the course of pregnancy is appreciable to support fetal growth and expansion of maternal blood volume. Dietary intake of iron generally cannot meet this demand, and all pregnant women should receive about 30 mg of elemental iron per day in the second and third trimesters. Oral iron therapy is commonly associated with GI side effects, such as nausea and constipation, and these symptoms often contribute to noncompliance. If supplementation is inadequate, however, anemia often becomes evident by the third trimester of pregnancy. Because iron deficiency is by far the most common cause of anemia in pregnancy, treatment is

usually empiric and consists of 60–100 mg of elemental iron per day and a diet containing iron-rich foods. Iron studies can confirm the diagnosis, if necessary (see Chapter 13), and further evaluation should be considered in patients who do not respond to oral iron. Intermittent iron supplementation (eg, every other day) has been associated with fewer side effects and may be reasonable for women who cannot tolerate daily therapy.

B. Folic Acid Deficiency Anemia

Megaloblastic anemia in pregnancy is almost always caused by folic acid deficiency, since vitamin B_{12} deficiency is uncommon in the childbearing years. Folate deficiency is usually caused by inadequate dietary intake of fresh leafy vegetables, legumes, and animal proteins.

The diagnosis is made by finding macrocytic red cells and hypersegmented neutrophils on a blood smear (see Chapter 13). However, blood smears in pregnancy may be difficult to interpret since they frequently show iron deficiency changes as well. With established folate deficiency, a supplemental dose of 1 mg/day and a diet with increased folic acid will generally correct the anemia.

C. Sickle Cell Anemia

Women with sickle cell anemia are subject to serious complications in pregnancy. The anemia becomes more severe, and acute pain crises often occur more frequently. When compared with women who do not have hemoglobinopathies, women with hemoglobin SS are at increased risk for infections (especially pulmonary and urinary tract), thromboembolic events, pregnancy-related hypertension, transfusion, cesarean delivery, preterm birth, and fetal growth restriction. There also continues to be an increased rate of maternal mortality, despite an increased recognition of the high-risk nature of these pregnancies. Intensive medical treatment may improve the outcomes for both mother and fetus. Prophylactically transfusing packed red cells to lower the level of hemoglobin S and elevate the level of hemoglobin A is a controversial practice without clear benefit. Most women with sickle cell disease will not require iron supplementation, but folate requirements can be appreciable due to red cell turnover from hemolysis.

D. Other Anemias

Although many of the inherited or acquired causes of anemia are relatively rare in women of childbearing age, they can be encountered in pregnancy. The implications for the mother and her offspring vary widely depending on the etiology of anemia. For example, mild microcytic anemia may be caused by iron deficiency, but it could also represent anemia of chronic disease because of previously undiagnosed malignancy. As such, women who have anemia caused by a disorder besides a nutritional deficiency are best managed in conjunction with a maternal-fetal medicine specialist and a hematologist. Additionally, women who have an inherited form of anemia (hemoglobinopathies and thalassemia syndromes, for example) should be offered genetic counseling; prenatal diagnosis, if available, should be discussed if the parents wish to know whether the fetus is affected.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 233: anemia in pregnancy. Obstet Gynecol. 2021;138:e55. [PMID: 34293770]
American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 78: hemoglobinopathies in pregnancy. Obstet Gynecol 2007;109:229. [Reaffirmed 2019] [PMID: 17197616]

ANTIPHOSPHOLIPID SYNDROME

The antiphospholipid syndrome (APS) is characterized by autoantibodies, notably in association with arterial and venous thrombosis and adverse pregnancy outcomes (see Chapter 20).

THYROID DISEASE

Thyroid disease is relatively common in pregnancy, and in their overt states, both hypothyroidism and hyperthyroidism have been consistently associated with adverse pregnancy outcomes. There are gestational age-specific effects that pregnancy has on thyroid function tests; failure to recognize these physiologic alterations can cause misclassification or misdiagnosis. Women who have a history of a thyroid disorder or symptoms that suggest thyroid dysfunction should be screened with thyroid function tests. Screening asymptomatic pregnant women, however, is of unproven benefit and is not currently recommended.

Overt hypothyroidism is defined by an elevated serum TSH level with a depressed FT_4 level. During pregnancy, several factors occur that affect maternal thyroid hormones: (1) Rising estrogen levels increase thyroxine binding globulin (TBG) serum concentrations, reducing FT_4 levels. (2) Placental deiodinase promotes the turnover of T_4. (3) Supplemental iron and prenatal multivitamins containing iron can bind to oral T_4 and reduce its intestinal absorption.

The most common etiology of hypothyroidism during pregnancy is Hashimoto (autoimmune) thyroiditis. Many of the symptoms of hypothyroidism mimic those of normal pregnancy, making its clinical identification difficult. Maternal hypothyroidism has consistently been associated with an increase in complications such as spontaneous abortion, preterm birth, preeclampsia, placental abruption, and impaired neuropsychological development in the offspring; the fetus is at least partially dependent on maternal T_4 for its CNS development—particularly in the second trimester. *Therefore, for women who need levothyroxine, it is prudent to increase the dosages by approximately 20–30% as soon as pregnancy is confirmed. Pregnant women with overt hypothyroidism or myxedema should be treated immediately with levothyroxine at full replacement doses of 1.6 mcg/kg/day (about 100–150 mcg daily).* For titration, the levothyroxine dosage may be increased according to clinical response and serum TSH, measuring serum TSH every 4–6 weeks and trying to keep the serum TSH level in a trimester-specific gestational reference range. An increase in the dose of levothyroxine may be required in the second

and third trimesters. By mid-pregnancy, women require an average of 47% increase in their levothyroxine dosage.

Subclinical hypothyroidism is defined as an increased serum TSH with a normal FT_4 level. Although some studies have found associations with untoward pregnancy outcomes such as miscarriage, preterm birth, and preeclampsia, others have failed to confirm these findings. There is no evidence that treatment of subclinical hypothyroidism will prevent any of these outcomes. The ACOG and the American Association of Clinical Endocrinologists recommend against universal screening for thyroid disease in pregnancy.

Overt hyperthyroidism, defined as excessive production of thyroxine with a depressed (usually undetectable) serum TSH level, is also associated with increased risks in pregnancy. Spontaneous pregnancy loss, preterm birth, preeclampsia, and maternal heart failure occur with increased frequency with untreated thyrotoxicosis. Thyroid storm, although rare, can be a life-threatening complication. Medical treatment of thyrotoxicosis is usually accomplished with the antithyroid drugs propylthiouracil or methimazole. Although teratogenicity has not been clearly established, in utero exposure to methimazole has been associated with aplasia cutis and choanal and esophageal atresia in the offspring of pregnancies so treated. Propylthiouracil is not believed to be teratogenic, but it has been associated with the rare complications of hepatotoxicity and agranulocytosis. Recommendations by the American Thyroid Association are to treat with propylthiouracil in the first trimester and convert to methimazole for the remainder of the pregnancy. The therapeutic target for the FT_4 level is the upper limit of the normal reference range. The TSH levels generally stay suppressed even with adequate treatment. A beta-blocker can be used for such symptoms as palpitations or tremors. Fetal hypothyroidism or hyperthyroidism is uncommon but can occur with maternal Graves disease, which is the most common cause of hyperthyroidism in pregnancy. *Radioiodine ablation is absolutely contraindicated in pregnancy because it may destroy the fetal thyroid as well.*

Postpartum thyroiditis is discussed in Chapter 26; see Thyroiditis.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 223: thyroid disease in pregnancy. Obstet Gynecol. 2020;135:e261 [PMID: 32443080]

DIABETES MELLITUS

Normal pregnancy can be characterized as a state of increased insulin resistance that helps ensure a steady stream of glucose delivery to the developing fetus. Thus, both mild fasting hypoglycemia and postprandial hyperglycemia are physiologic. These metabolic changes are felt to be hormonally mediated with likely contributions from human placental lactogen, estrogen, and progesterone.

A. Gestational Diabetes Mellitus

Gestational diabetes mellitus is abnormal glucose tolerance in pregnancy and is generally believed to exaggerate the pregnancy-induced physiologic changes in carbohydrate metabolism. Alternatively, pregnancy may unmask an underlying propensity for glucose intolerance, which will be evident in the nonpregnant state at some future time if not in the immediate postpartum period. Indeed, at least 50% of women with gestational diabetes will have an overt diabetes diagnosis at some point in their lifetime. During the pregnancy, the principal concern in women identified to have gestational diabetes is excessive fetal growth, which can cause increased maternal and perinatal morbidity. Shoulder dystocia occurs more frequently in infants of mothers with diabetes because of fetal overgrowth and increased fat deposition on the shoulders. Cesarean delivery and preeclampsia are also significantly increased in women with diabetes, both gestational and overt.

All asymptomatic pregnant women should undergo laboratory screening for gestational diabetes after 24 weeks' gestation. The diagnostic thresholds for glucose tolerance tests in pregnancy are not universally agreed upon, and importantly, adverse pregnancy outcomes appear to occur along a continuum of glucose intolerance even if the diagnosis of gestational diabetes is not formally assigned. A two-stage testing strategy is recommended by the ACOG, starting with a 50-g screening test offered to all pregnant women at 24–28 weeks' gestation. If this test is abnormal, the diagnostic test is a 100-g oral glucose tolerance test (Table 19–4).

Women in whom gestational diabetes is diagnosed should undergo nutrition counseling, and medications are typically initiated for those with persistent fasting hyperglycemia. Insulin has historically been considered the standard medication used to achieve glycemic control. Oral hypoglycemic agents, principally glyburide and metformin, have been evaluated in short-term clinical trials and appear to achieve similar degrees of glycemic control to insulin without increasing maternal or neonatal morbidity. These medications, however, have not been approved by the US FDA for this indication; the long-term safety of oral agents has not been adequately studied in the women

Table 19–4. Screening and diagnostic criteria for gestational diabetes mellitus.

Screening for gestational diabetes mellitus
1. 50-g oral glucose load, administered between 24 and 28 weeks, without regard to time of day or time of last meal.
2. Venous plasma glucose measured 1 hour later.
3. Value of 140 mg/dL (7.8 mmol/L) or above in venous plasma indicates the need for a diagnostic glucose tolerance test.
Diagnosis of gestational diabetes mellitus
1. 100-g oral glucose load, administered in the morning after overnight fast lasting at least 8 hours but not more than 14 hours, and following at least 3 days of unrestricted diet (> 150 g carbohydrate) and physical activity.
2. Venous plasma glucose is measured fasting and at 1, 2, and 3 hours. Patient should remain seated and should not smoke throughout the test.
3. The diagnosis of gestational diabetes is made when two or more of the following venous plasma concentrations are met or exceeded: fasting, 95 mg/dL (5.3 mmol/L); 1 hour, 180 mg/dL (10 mmol/L); 2 hours, 155 mg/dL (8.6 mmol/L); 3 hours, 140 mg/dL (7.8 mmol/L).

or in their offspring, and study quality of these agents has been poor. The current standard of care is insulin, unless circumstances preclude its use. In those cases, metformin is a reasonable choice. Insulin regimens commonly include multiple daily injections of a split-dose mix of intermediate-acting and short-acting agents. Regular and NPH insulins, as well as insulin lispro and aspart, do not cross the placenta. Once therapy is initiated, blood glucose surveillance is important to assess for adequacy of glycemic control. Capillary blood glucose levels should be checked four times per day, once fasting and three times after meals. Euglycemia is considered to be 60–90 mg/dL (3.3–5.0 mmol/L) while fasting and less than 120 mg/dL (6.7 mmol/L) 2 hours postprandially. Intensive therapy with dietary modifications or insulin therapy, or both, has been demonstrated to decrease rates of macrosomia, shoulder dystocia, and preeclampsia. Because of the increased prevalence of overt diabetes in women identified to have gestational diabetes, they should be screened at 6–12 weeks' postpartum with a fasting plasma glucose test or a 2-hour oral glucose tolerance test (75-g glucose load).

B. Overt Diabetes Mellitus

Overt diabetes is diabetes mellitus that antedates the pregnancy. There is an inverse relationship between glycemic control and fetal malformations, and women whose periconceptional glycosylated hemoglobin levels are at or near normal levels have rates of malformations that approach baseline. In gestational diabetes, fetal overgrowth from inadequately controlled hyperglycemia remains a significant concern because of the increased maternal and perinatal morbidity that accompany macrosomia. Women with overt diabetes are subject to several other complications as well. Spontaneous pregnancy loss and third-trimester stillbirths occur with increased frequency in these women. There is also at least a twofold to threefold increased risk for fetal malformations (risk in in normal pregnancies is 2–3%), as hyperglycemia during organogenesis is teratogenic. The most common malformations in offspring of diabetic women are cardiac, skeletal, and neural tube defects. For the mother, the likelihood of infections and pregnancy-related hypertension is increased.

Preconception counseling and evaluation in a diabetic woman is ideal to maximize the pregnancy outcomes. This provides an opportunity to optimize glycemic control and evaluate for evidence of end-organ damage. The initial evaluation of diabetic women should include a complete chemistry panel, HbA_{1c} determination, 24-hour urine collection for total protein and creatinine clearance, funduscopic examination, and an ECG. Hypertension is common and may require treatment. Optimally, euglycemia should be established before conception and maintained during pregnancy with daily home glucose monitoring by the patient. A well-planned dietary program is a key component, with an intake of 1800–2200 kcal/day divided into three meals and three snacks. Insulin is given subcutaneously in a split-dose regimen as described above for women with gestational diabetes. The use of continuous insulin pump therapy may be helpful for some patients (see Chapter 27).

Throughout the pregnancy, diabetic women should be seen every 2–3 weeks and more frequently depending on the clinical condition. Adjustments in the insulin regimen may be necessary as the pregnancy progresses to maintain optimal glycemic control. A specialized ultrasound is often performed around 20 weeks to screen for fetal malformations. Symptoms and signs of infections should be evaluated and promptly treated. In the third trimester, fetal surveillance is indicated, and women with diabetes should receive serial antenatal testing (usually in the form of a nonstress test or biophysical profile). The timing of delivery is dictated by the quality of diabetic control, the presence or absence of medical complications, and fetal status. The goal is to reach 39 weeks (38 completed weeks) and then proceed with delivery. Confirmation of lung maturity may be appropriate if preterm delivery is contemplated.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 201: pregestational diabetes mellitus. Obstet Gynecol. 2018;132:e228. [PMID: 30461693]

American College of Obstetricians and Gynecologists. Practice Bulletin No. 190: gestational diabetes mellitus. Obstet Gynecol. 2018;131:e49. [PMID: 29370047]

CHRONIC HYPERTENSION

Chronic hypertension is estimated to complicate up to 5% of pregnancies. To establish this diagnosis, hypertension should antedate the pregnancy or be evident before 20 weeks' gestation to differentiate it from pregnancy-related hypertension. This distinction can be problematic when the initial presentation is after 20 weeks, but chronic hypertension is confirmed if the blood pressure remains elevated beyond 12 weeks postpartum. Risk factors for chronic hypertension include older maternal age, Black race, and obesity.

Women with chronic hypertension are at increased risk for adverse maternal and perinatal outcomes. Superimposed preeclampsia develops in up to 20% of women with mild hypertension, but the risk increases up to 50% when there is severe baseline hypertension (160/110 mm Hg or higher) and may be even higher when there is evidence of end-organ damage. When preeclampsia is superimposed on chronic hypertension, there is a tendency for it to occur at an earlier gestational age, be more severe, and impair fetal growth. Women with chronic hypertension are also at increased risk for placental abruption, cesarean delivery, preterm birth, and perinatal mortality.

Ideally, women with chronic hypertension should undergo a preconceptional evaluation to detect end-organ damage, assess the need for antihypertensive therapy, and discontinue teratogenic medications. The specific tests ordered may vary depending on the severity of the hypertensive disorder, but an evaluation of liver, kidney, and cardiac function (eg, 24-hour urine protein and maternal echocardiogram if mother takes medications) is appropriate.

If the woman is not known to have chronic hypertension, then initiation of antihypertensive therapy in pregnant women is indicated only if the blood pressure is sustained at or above 160/110 mm Hg or if there is

evidence of end-organ damage. Treatment of hypertension has not been demonstrated to improve pregnancy outcomes, but it is indicated in women with significant hypertension for long-term maternal cardiovascular health. Although methyldopa (Table 11–10) has the longest record of safety in pregnancy, nifedipine (Table 11–7) and labetalol (Table 11–9) are also acceptable, and these three agents are recommended above all others when initiating therapy in pregnancy. Care must be taken not to excessively reduce the blood pressure, as this may decrease uteroplacental perfusion. The goal is a modest reduction in blood pressure and avoidance of severe hypertension.

If a woman with mild chronic hypertension is stable on a medical regimen when she becomes pregnant, it is usually appropriate to continue this therapy, although the benefits of doing so are not well established. *ACE inhibitors and ARBs, however, are contraindicated in all trimesters of pregnancy*. These medications are teratogenic in the first trimester and cause fetal hypocalvaria and AKI in the second and third trimesters.

When there is sustained severe hypertension despite multiple medications or significant end-organ damage from hypertensive disease, pregnancy is not likely to be tolerated well. In these situations, therapeutic abortion may be appropriate. If the pregnancy is continued, the woman must be counseled that the maternal and perinatal risks are appreciable, and complications such as superimposed preeclampsia and fetal growth restriction should be anticipated.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 203: chronic hypertension in pregnancy. Obstet Gynecol. 2019;133:e26. [PMID: 30575676]

HEART DISEASE

Normal pregnancy physiology is characterized by cardiovascular adaptations in the mother. Cardiac output increases markedly because of both augmented stroke volume and an increase in the resting heart rate, and the maternal blood volume expands by up to 50%. These changes may not be tolerated well in women with functional or structural abnormalities of the heart. Thus, although only a small number of pregnancies are complicated by cardiac disease, these contribute disproportionately to overall rates of maternal morbidity and mortality. Most cardiac disease in women of childbearing age in the United States is caused by congenital heart disease and not rheumatic heart disease. Ischemic heart disease, however, is being seen more commonly in pregnant women due to increasing rates of comorbid conditions, such as diabetes mellitus, hypertension, and obesity.

For practical purposes, the best single measurement of cardiopulmonary status is defined by the New York Heart Association Functional Classification. Most pregnant women with cardiac disease have class I or II functional disability, and although good outcomes are generally anticipated in this group, complications such as preeclampsia, preterm birth, and low birth weight appear to occur with increased frequency. Women with more severe disability (class III or IV) are rare in contemporary obstetrics; however, the maternal mortality is markedly increased in this setting and is usually the result of heart failure. Because of these risks, therapeutic abortion for maternal health should be considered in women who are severely disabled from cardiac disease. Specific conditions that have been associated with a high risk for maternal death include Eisenmenger syndrome, primary pulmonary hypertension, Marfan syndrome with aortic root dilatation, and severe aortic or mitral stenosis. In general, these conditions should be considered contraindications to pregnancy.

The importance of preconceptional counseling for women with heart disease cannot be overstated. A thorough evaluation before pregnancy provides an opportunity for comprehensive risk assessment and detailed planning. Once pregnant, women with cardiac disease are best treated by a team of practitioners with experience in caring for such patients. Heart failure and arrhythmias are the most common cardiovascular complications associated with heart disease in pregnancy, and adverse maternal and fetal outcomes are increased when they occur. Symptoms of volume overload should therefore be evaluated and treated promptly. Labor management depends on the underlying cardiac lesion and the degree of disability. Women with a history of arrhythmia should have continuous cardiac monitoring throughout labor, delivery, and the immediate postpartum period. Cesarean delivery is generally reserved for obstetric indications but may be appropriate for women in whom Valsalva maneuvers are contraindicated. The early postpartum period is a critical time for fluid management. Patients who are predisposed to heart failure should be monitored closely during the puerperium.

Infective endocarditis prophylaxis is not recommended for a vaginal or cesarean delivery in the absence of infection, except in the small subset of patients at highest risk for adverse outcomes from endocarditis. The women at highest risk include those with cyanotic heart disease, prosthetic valves, or both. Prophylactic antibiotics for endocarditis, if required, should be given intravenously (see Table 33–5). If infection is present, such as chorioamnionitis, the underlying infection should be treated with the usual regimen and additional agents are not needed specifically for endocarditis prophylaxis.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 199: use of prophylactic antibiotics in labor and delivery. Obstet Gynecol. 2018;132:e103. [PMID: 30134425]
Canobbio MM et al. Management of pregnancy in patients with complex congenital heart disease: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2017;135:e50. [PMID: 28082385]

ASTHMA

(See also Chapter 9.**)**

Asthma is one of the most common medical conditions encountered in pregnancy. Women with mild to moderate asthma can generally expect excellent pregnancy outcomes, but severe or poorly controlled asthma has been

associated with several pregnancy complications, including preterm birth, small-for-gestational-age infants, and preeclampsia. The effects of pregnancy on asthma are likely minimal as asthma severity in the pregnancy has been reported to be similar to its severity during the year preceding the pregnancy. Strategies for treatment are similar to those in nonpregnant women. Patients should be educated about symptom management and avoidance of asthma triggers. Baseline pulmonary function tests can objectively assess lung function and may help the patient with self-monitoring of her asthma severity using a peak flow meter. As in nonpregnant women, treatment algorithms generally follow a stepwise approach, and commonly used medications, particularly those for mild to moderate asthma symptoms, are generally considered safe in pregnancy. Concerns about teratogenicity and medication effects on the fetus should be thoroughly discussed with the patient to decrease noncompliance rates. Inhaled beta-2-agonists are indicated for all asthma patients, and low to moderate dose inhaled corticosteroids are added for persistent symptoms when a rescue inhaler alone is inadequate. Systemic corticosteroid administration is reserved for severe exacerbations but should not be withheld, if indicated, irrespective of gestational age. Cromolyn, leukotriene receptor antagonists, and theophylline are appropriate alternative therapies if first-line management is ineffective. The primary goals of management in pregnancy include minimizing symptoms and avoiding hypoxic episodes to the fetus. Prostaglandin F2a and ergonovine—medications frequently used to treat postpartum uterine atony—should be avoided because they can precipitate bronchospasm in women with asthma.

American College of Obstetricians and Gynecologists. Practice Bulletin No. 90: asthma in pregnancy. Obstet Gynecol. 2008;111:457. [Reaffirmed 2019] [PMID: 18238988]

SEIZURE DISORDERS

Epilepsy is one of the most common serious neurologic disorders in pregnant women. Many of the commonly used antiepileptic drugs are known human teratogens. Therefore, the principal objectives in managing pregnancy in epileptic women are achieving adequate control of seizures while minimizing exposure to medications that can cause congenital malformations. Certain women who are contemplating pregnancy and have been seizure-free for 2–5 years may be considered candidates for discontinuation of antiseizure medication before pregnancy. For those who continue to require treatment, however, therapy with one medication is preferred. Selecting a regimen should be based on the type of seizure disorder and the risks associated with each medication. Valproic acid should not be considered first-line therapy because it has consistently been associated with higher rates of fetal malformations than most other commonly used antiepileptic drugs, and it may be associated with impaired neurocognitive development in the offspring. Phenytoin and carbamazepine both have established patterns of associated fetal malformations. Concerns about teratogenicity have prompted increasing use of the newer antiepileptic drugs such as lamotrigine, topiramate, oxcarbazepine, and levetiracetam. Although the safety of these medications in pregnancy continues to be evaluated, experiences from ongoing registries and large, population-based studies suggest that in utero exposure to the newer antiepileptic drugs in the first trimester of pregnancy carries a lower risk of major malformations than older medications. Lamotrigine and levetiracetam are considered the least teratogenic. One birth registry, however, found an increase in oral clefts among women taking lamotrigine. Several small studies have found an association between levetiracetam and low birth weight. Some studies suggest that topiramate is associated with a slightly increased risk of oral clefts. Although it is recommended that pregnant women with epilepsy be given supplemental folic acid, it is unclear if supplemental folate decreases rates of fetal malformations in women taking anticonvulsant therapy. Antiepileptic medications may be affected by volume of distribution changes in pregnancy, and serum levels should be followed when appropriate.

American College of Obstetricians and Gynecologists. Clinical Updates in Women's Health Care: Seizures. 2021 Jan 1. https://www.acog.org/clinical/journals-and-publications/clinical-updates/2021/01/seizures

Harden C et al. Epilepsy in pregnancy. Neurol Clin. 2019;37:53. [PMID: 30470275]

INFECTIOUS CONDITIONS COMPLICATING PREGNANCY

URINARY TRACT INFECTION

The urinary tract is especially vulnerable to infections during pregnancy because the altered secretions of steroid sex hormones and the pressure exerted by the gravid uterus on the ureters and bladder cause hypotonia and congestion and predispose to urinary stasis. Labor and delivery and urinary retention postpartum also may initiate or aggravate infection. *Escherichia coli* is the offending organism in over two-thirds of cases.

From 2% to 15% of pregnant women have asymptomatic bacteriuria, which some believe to be associated with an increased risk of preterm birth. It is estimated that pyelonephritis will develop in 20–40% of these women if untreated.

An evaluation for asymptomatic bacteriuria at the first prenatal visit is recommended for all pregnant women. If a urine culture is positive, treatment should be initiated. Nitrofurantoin (100 mg orally twice daily), ampicillin (250 mg orally four times daily), and cephalexin (250 mg orally four times daily) are acceptable medications for 4–7 days. Sulfonamides should be avoided in the third trimester because they may interfere with bilirubin binding and thus impose a risk of neonatal hyperbilirubinemia and kernicterus. Fluoroquinolones are also contraindicated because of their potential teratogenic effects on fetal cartilage and bone. Patients with recurrent bacteriuria should receive suppressive medication (once daily dosing of an appropriate antibiotic) for the remainder of the pregnancy. Acute

pyelonephritis requires hospitalization for intravenous administration of antibiotics and crystalloids until the patient is afebrile; this is followed by a full course of oral antibiotics.

Kalinderi K et al. Urinary tract infection during pregnancy: current concepts on a common multifaceted problem. J Obstet Gynaecol. 2018;38:448. [PMID: 29402148]

GROUP B STREPTOCOCCAL INFECTION

Group B streptococci frequently colonize the lower female genital tract, with an asymptomatic carriage rate in pregnancy of 10–30%. This rate depends on maternal age, gravidity, and geographic variation. Vaginal carriage is asymptomatic and intermittent, with spontaneous clearing in approximately 30% and recolonization in about 10% of women. Adverse perinatal outcomes associated with group B streptococcal colonization include UTI, intrauterine infection, premature rupture of membranes, preterm delivery, and postpartum metritis.

Women with postpartum metritis due to infection with group B streptococci, especially after cesarean section, develop fever, tachycardia, and abdominal pain, usually within 24 hours after delivery. Approximately 35% of these women are bacteremic.

Group B streptococcal infection is a common cause of neonatal sepsis. Transmission rates are high, yet the rate of neonatal sepsis is surprisingly low at less than 1:1000 live births. Unfortunately, the mortality rate associated with early-onset disease can be as high as 20–30% in premature infants. In contrast, it is approximately 2–3% in those at term. Moreover, these infections can contribute markedly to chronic morbidity, including developmental delays and neurologic disabilities. Late-onset disease develops through contact with hospital nursery personnel. Up to 45% of these health care workers can carry the bacteria on their skin and transmit the infection to newborns.

The 2019 ACOG recommendations for screening and prophylaxis for group B streptococcal colonization are available at https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/02/prevention-of-group-b-streptococcal-early-onset-disease-in-newborns.

VARICELLA

Commonly known as chickenpox, varicella-zoster virus (VZV) infection has a fairly benign course when incurred during childhood but may cause serious illness in adults, particularly during pregnancy. Infection results in lifelong immunity. Approximately 95% of women born in the United States have VZV antibodies by the time they reach reproductive age. The incidence of VZV infection during pregnancy has been reported as up to 7:10,000. *The vaccine is contraindicated in pregnancy because the effects of the vaccine on the fetus are unknown.* Nonpregnant women who are vaccinated should avoid pregnancy for 1 month after injection. Inadvertent vaccination in early pregnancy or within a month of pregnancy is not an indication for termination, although women should be counseled about theoretical risks.

Clinical Findings

A. Symptoms and Signs

The incubation period for this infection is 10–20 days. A primary infection follows and is characterized by a flu-like syndrome with malaise, fever, and development of a pruritic maculopapular rash on the trunk, which becomes vesicular and then crusts. Pregnant women are prone to the development of VZV pneumonia, often a fulminant infection sometimes requiring respiratory support. After primary infection, the virus becomes latent, ascending to dorsal root ganglia. Subsequent reactivation can occur as zoster, often under circumstances of immunocompromise, although this is rare during pregnancy.

Two types of fetal infection have been documented. The first is congenital VZV syndrome, which typically occurs in 0.4–2% of fetuses exposed to primary VZV infection during the first trimester. Anomalies include limb and digit abnormalities, microphthalmos, and microcephaly.

Infection during the second and third trimesters is less threatening. Maternal IgG crosses the placenta, protecting the fetus. The only infants at risk for severe infection are those born after maternal viremia but before development of maternal protective antibody. Maternal infection manifesting 5 days before or up to 2 days after delivery is the time period believed to be most hazardous for transmission to the fetus.

B. Laboratory Findings

Diagnosis is commonly made on clinical grounds. Laboratory verification is made by ELISA, fluorescent antibody, and hemagglutination inhibition antibody techniques. Vesicular fluid can be sent for qualitative varicella PCR assay.

Treatment

Varicella-zoster immune globulin (VZIG) has been shown to prevent or modify the symptoms of infection in exposed persons. Treatment success depends on identification of susceptible women at or just following exposure. Exposed women with a questionable or negative history of chickenpox should be checked for antibody, since the overwhelming majority will have been previously exposed. If the antibody is negative, VZIG (625 units intramuscularly) should ideally be given within 96 hours of exposure for greatest efficacy, but the CDC reports it can be given for up to 10 days. There are no known adverse effects of VZIG administration during pregnancy, although the incubation period for disease can be lengthened. Infants born to women in whom symptoms develop in the period from 5 days before delivery to 2 days after delivery should also receive VZIG (125 units).

Pregnant women with varicella may benefit from treatment with oral acyclovir, 800 mg orally four times daily for 5 days, if started within 24 hours of rash onset. Treatment has been shown to improve maternal symptoms but does not prevent congenital varicella. Infected pregnant women should be closely observed and hospitalized at the earliest signs of pulmonary involvement. Intravenous acyclovir (10 mg/kg intravenously every 8 hours) is recommended in the treatment of VZV pneumonia.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 151: cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy. Obstet Gynecol. 2015;125:1510. [Reaffirmed 2019] [PMID: 26000539]

TUBERCULOSIS

The diagnosis of tuberculosis in pregnancy is made by history taking, physical examination, and testing, with special attention to women in high-risk groups. Women at high risk include those from endemic areas, those infected with HIV, drug users, health care workers, and close contacts of people with tuberculosis. Screening chest radiographs should only be obtained in pregnant patients who have a positive test or with suggestive findings in the history and physical examination. Abdominal shielding must be used if a chest radiograph is obtained. Both tuberculin skin testing and interferon gamma release assays are acceptable tests in pregnancy.

Decisions on treatment depend on whether the patient has active disease or is at high risk for progression to active disease. Pregnant women with active disease or who are high risk for progression should be treated during pregnancy as the risks of complications from tuberculosis outweigh the risks of treatment. Pregnant women with latent disease not at high risk for disease progression can receive treatment postpartum, which does not preclude breastfeeding. The concentration of medication in breast milk is neither toxic nor adequate for treatment of the newborn. Isoniazid, ethambutol, and rifampin are used to treat tuberculosis (see Chapters 9 and 33). Because isoniazid therapy may cause vitamin B_6 deficiency, a supplement of 50 mg/day of vitamin B_6 should be given simultaneously. There is concern that isoniazid, particularly in pregnant women, can cause hepatitis. Liver biochemical tests should be performed monthly in pregnant women who receive treatment. Streptomycin, ethionamide, and most other antituberculous drugs should be avoided in pregnancy. If adequately treated, tuberculosis in pregnancy has an excellent prognosis.

Miele K et al. Tuberculosis in pregnancy. Obstet Gynecol. 2020; 135:1444. [PMID: 32459437]

HIV/AIDS DURING PREGNANCY

Asymptomatic HIV infection is associated with a normal pregnancy rate and no increased risk of adverse pregnancy outcomes. There is no evidence that pregnancy causes AIDS progression.

Previously, two-thirds of HIV-positive neonates acquired their infection close to, or during, the time of delivery. Routine HIV screening in pregnancy, including the use of rapid HIV tests in Labor and Delivery units, and using antiretroviral drugs has markedly reduced this transmission risk to approximately 1%. In an HIV-positive pregnant woman, a CD4 count, plasma RNA level, and resistance testing (if virus is detectable, and the patient has not already had this) should be obtained at the first prenatal visit. Treatment should not be delayed while waiting for the results of resistance testing. Prior or current antiretroviral use should be reviewed. The patient should be tested for HLA-B*5701 if abacavir may be prescribed; HLA-B*5701 positivity puts the patient at risk for a serious hypersensitivity reaction and its use is contraindicated.

A woman already taking and tolerating an acceptable antiretroviral regimen need not discontinue it in the first trimester. Patients should also be tested for hepatitis A, hepatitis C, tuberculosis, toxoplasmosis, and cytomegalovirus.

Women not taking medication should be offered combination antiretroviral therapy (commonly a dual nucleoside reverse transcriptase inhibitor combination and either a ritonavir-boosted protease inhibitor or an integrase strand transfer inhibitor) after counseling regarding the potential impact of therapy on both mother and fetus (see Chapter 31). Antiretroviral therapy should be offered regardless of viral load and CD4 count. Whether to start in the first or second trimester should be determined on a case-by-case basis, but it should be started as early as reasonably possible. It can be started in the first trimester after explanation of risks and benefits, provided the mother is not experiencing nausea and vomiting. Most medications used to treat HIV/AIDS have thus far proven to be safe in pregnancy with an acceptable risk/benefit ratio. The physiologic changes that occur during pregnancy may alter the effect of some medications. Before starting any regimen, the safety and efficacy of the medications selected should be reviewed. Standard of care also includes administration of intravenous zidovudine (2 mg/kg intravenously over 1 hour followed by 1 mg/kg/hour intravenously) begun 3 hours before cesarean delivery and continued through the surgery until cord clamping in women whose viral load near delivery (after 34–36 weeks' gestation or within 4–6 weeks of delivery) is more than 1000 copies/mL or unknown. Antiretroviral therapy on the patient's usual schedule should be continued in labor. Intravenous zidovudine is not required for antiretroviral therapy–compliant women whose viral load is less than or equal to 50 copies/mL near delivery; data are limited in cases where the viral load is between 50 copies/mL and 1000 copies/mL.

The use of prophylactic elective cesarean section at 38 weeks' gestation (before the onset of labor or rupture of the membranes) to prevent vertical transmission of HIV infection from mother to fetus has been shown to further reduce the transmission rate. In patients with a viral load of less than 1000 copies/mL near delivery, there may be no additional benefit of cesarean delivery, and those women can be offered a vaginal delivery. Amniotomy should not be performed in the setting of viremia unless there is a clear obstetric indication. Amniotomy, however, has not been associated with an increased risk of perinatal transmission when the mother is receiving antiretroviral therapy and virologically suppressed. Internal monitors, particularly the fetal scalp electrode, should be avoided as should operative deliveries (forceps-assisted and vacuum-assisted vaginal deliveries). Methergine (used for postpartum hemorrhage) should be avoided, if possible, in patients receiving regimens that include cytochrome P450 (CYP) 3A4 inhibitors and CYP3A4 enzyme inducers. HIV-infected women should be advised not to breastfeed their infants.

The Public Health Task Force provides guidelines for the management of HIV/AIDS in pregnancy (https://hivinfo.nih.gov). In addition, there is the National Perinatal HIV Hotline, which provides free consultation regarding perinatal HIV care (1-888-448-8765).

Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. 2021 Dec 30. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Perinatal_GL.pdf

MATERNAL HEPATITIS B & C CARRIER STATE

A. Hepatitis B Virus

There are an estimated 350 million chronic carriers of hepatitis B virus worldwide. In the United States, 1.4 million people are infected, with the highest rate among Asian American persons. All pregnant women should be screened for HBsAg. Transmission of the virus to the baby after delivery is likely if both surface antigen and e antigen are positive. Vertical transmission can be blocked by the immediate postdelivery administration to the newborn of hepatitis B immunoglobulin and hepatitis B vaccine intramuscularly. The vaccine dose is repeated at 1 and 6 months of age. Third trimester administration of tenofovir disoproxil fumarate, 300 mg orally once per day starting at 28–32 weeks and continuing through delivery (first line), lamivudine, or telbivudine to women with a viral load of greater than 10^6–10^8 copies/mL has been shown to reduce vertical transmission particularly if the viral load is less than 10^6 copies/mL at delivery. This therapy appears safe in pregnancy although long-term follow-up data are lacking. Pregnant women with chronic hepatitis B should have liver biochemical tests and viral load testing during the pregnancy. Hepatitis B infection is not a contraindication to breastfeeding, and antiviral therapy if given need not be continued postpartum.

B. Hepatitis C Virus

This infection is the most common chronic blood-borne infection in the United States. Because risk-based screening misses approximately 50% of cases and postpartum treatment is highly effective, universal screening in pregnancy is recommended. The average rate of hepatitis C virus (HCV) infection among infants born to HCV-positive, HIV-negative women is 5–6%. However, the average infection rate increases to 10–11% when mothers are coinfected with HCV and HIV. The principal factor associated with transmission is HCV RNA in the mother at the time of birth. Treatment is not recommended in pregnancy. Interferon and ribavirin have been considered contraindicated. Ledipasvir/sofosbuvir (Harvoni) has been shown to be safe in animal studies. Direct-acting antiviral regimens should only be initiated during pregnancy if in the setting of a clinical trial. Cesarean section is not recommended solely for a maternal history of hepatitis C. During labor, early rupture of membranes and placement of a fetal scalp electrode should be avoided if safe to do so because of the unknown risk of increased vertical transmission. Breastfeeding is not contraindicated.

Dotters-Katz SK et al. Society for Maternal-Fetal Medicine Consult Series No. 56: hepatitis C in pregnancy-updated guidelines: replaces Consult No. 43. Am J Obstet Gynecol. 2021; 225:B8. [PMID: 34116035]

Jin J. JAMA patient page. Screening for hepatitis B in pregnant women. JAMA. 2019;322:376. [PMID: 31334796]

HERPES GENITALIS

Infection of the lower genital tract by herpes simplex virus type 2 (HSV-2) (see also Chapter 6) is a common STD with potentially serious consequences to pregnant women and their newborn infants. Although up to 25% of pregnant women may have antibodies to HSV-2, a history of the infection is unreliable, and the incidence of neonatal infection is not known. There are estimated to be 1200–1500 cases of neonatal infection annually in the United States. Many infected neonates are born to women with no history, symptoms, or signs of infection.

Women who have had *primary* herpes infection late in pregnancy are at high risk for shedding virus at delivery; however, it can be difficult to differentiate primary from nonprimary infection. Women with a primary infection or nonprimary first outbreak and women with a clinical history of genital herpes should be offered prophylactic acyclovir, 400 mg orally three times daily, starting at 36 weeks' gestation, to decrease the likelihood of active lesions at the time of labor and delivery. For treatment, see Chapter 32.

Women with a history of *recurrent* genital herpes have a lower neonatal attack rate than women infected during the pregnancy, but they should still be monitored with clinical observation and culture of any suspicious lesions. Since asymptomatic viral shedding is not predictable by antepartum cultures, recommendations do not include routine cultures in individuals with a history of herpes without active disease. However, when labor begins, vulvar and cervical inspection should be performed. Cesarean delivery is indicated at the time of labor if there are prodromal symptoms or active genital lesions.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 220: management of genital herpes in pregnancy. Obstet Gynecol. 2020;135:e193. [PMID: 32332414]

SYPHILIS, GONORRHEA, & *CHLAMYDIA TRACHOMATIS* INFECTION

These STDs have significant consequences for mother and child (see also Chapters 33 and 34). Untreated syphilis in pregnancy can cause late abortion, stillbirth, transplacental infection, and congenital syphilis. Gonorrhea can produce large-joint arthritis by hematogenous spread as well as ophthalmia neonatorum. Maternal chlamydial infections are largely asymptomatic but are manifested in the newborn by inclusion conjunctivitis and, at age 2–4 months, by pneumonia. The diagnosis of each can be reliably made by appropriate laboratory tests. All women should be tested

for syphilis as part of their routine prenatal care. Pregnant women younger than 25 years and those at increased risk for *C trachomatis* should be screened for chlamydia at their first prenatal visit. Repeat testing depends on risk factors, prevalence, and state laws. A pregnant woman treated for *C trachomatis* should be tested for cure 4 weeks later and then retested 3 months later because of high reinfection rates. Women who remain at high risk should be tested in the third trimester. Women younger than 25 years and those at increased risk should be tested for gonorrhea at their first prenatal appointment. Women with positive tests for gonorrhea should be treated and then retested 3 months later. Women who remain at high risk should be tested in the third trimester. The sexual partners of women with STDs should be identified and treated if possible; the local health department can assist with this process.

Workowski KA et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021:70:1. [PMID: 34292926]

GASTROINTESTINAL, HEPATIC, & BILIARY DISORDERS OF PREGNANCY

Complications involving the GI tract, liver, and gallbladder are common in pregnancy. Nausea and vomiting in the first trimester affect most pregnant women to some degree (see Obstetric Complications of the First & Second Trimesters). *Nausea and vomiting in the last half of pregnancy, however, are never normal;* a thorough evaluation of such complaints is mandatory. Some of these conditions are incidental to pregnancy (eg, appendicitis), while others are related to the gravid state and tend to resolve with delivery (eg, acute fatty liver of pregnancy). Importantly, the myriad anatomic and physiologic changes associated with normal pregnancy must be considered when assessing for a disease state. Likewise, interpretation of laboratory studies must consider the pregnancy-associated changes in hepatic protein production.

For conditions in which surgery is clinically indicated, operative intervention should never be withheld based solely on a woman being pregnant. While purely elective surgery is avoided during pregnancy, women who undergo surgical procedures for an urgent or emergent indication during pregnancy do not appear to be at increased risk for adverse outcomes. Obstetric complications, when they occur, are more likely to be associated with the underlying maternal illness. Recommendations have held that the optimal time for semi-elective surgery is the second trimester to avoid exposure to anesthesia in the first trimester and the enlarged uterus in the third. Importantly, however, there is no convincing evidence that general anesthesia induces malformations or increases the risk for abortion.

CHOLELITHIASIS & CHOLECYSTITIS

Cholelithiasis is common in pregnancy as physiologic changes such as increased cholesterol production and incomplete gallbladder emptying predispose to gallstone formation. The diagnosis is usually suspected based on classic symptoms of nausea, vomiting, and right upper quadrant pain, usually after meals, and is confirmed with right upper quadrant ultrasound. Symptomatic cholelithiasis without cholecystitis is usually managed conservatively, but recurrent symptoms are common. Cholecystitis results from obstruction of the cystic duct and often is accompanied by bacterial infection. Medical management with antibiotics is reasonable in selected cases, but definitive treatment with cholecystectomy will help prevent complications such as gallbladder perforation and pancreatitis. Cholecystectomy has successfully been performed in all trimesters of pregnancy and should not be withheld based on the stage of pregnancy if clinically indicated. Laparoscopy is preferred in the first half of pregnancy but becomes more technically challenging in the last trimester due to the enlarged uterus and cephalad displacement of abdominal contents.

Obstruction of the common bile duct, which can lead to cholangitis, is an indication for surgical removal of gallstones and establishment of biliary drainage. Endoscopic retrograde cholangiopancreatography (ERCP) with or without sphincterotomy is a nonsurgical alternative. ERCP should only be undertaken when there is therapeutic intent. Pregnant women can safely undergo ERCP provided that precautions are taken to minimize fetal exposure to radiation. There does, however, appear to be a slightly higher rate of post-procedure pancreatitis in pregnant women who undergo ERCP. Magnetic resonance cholangiopancreatography (MRCP) can also be of use in patients with suspected common bile duct obstruction. This study is useful for those women in whom the etiology of common duct dilatation is unclear on ultrasound. MRCP can provide detailed evaluation of the entire biliary system and the pancreas while avoiding ionizing radiation.

The most common cause of acute pancreatitis in pregnancy is gallstone disease. The diagnosis can be confirmed with an appropriate history and an elevated serum amylase or lipase. Although pregnancy is associated with a rise in serum amylase, a value of at least two times the upper limit of normal suggests pancreatitis with the appropriate clinical scenario. Management is conservative, including bowel rest, intravenous fluids, supplemental nutrition if necessary, and analgesics. CT imaging should be avoided unless severe complications such as necrosis, abscess, or hemorrhage are suspected.

Abushamma S et al. A guide to upper gastrointestinal tract, biliary, and pancreatic disorders: clinical updates in women's health care primary and preventive care review. Obstet Gynecol. 2021;137:1152. [PMID: 34011887]

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy, a disorder limited to the gravid state, occurs in the third trimester of pregnancy and causes acute hepatic failure. With improved recognition and immediate delivery, the maternal mortality rate in contemporary reports is about 4%. The disorder is usually seen after the 35th week of gestation and is more common in primigravidas and those with twins. The incidence is about 1:10,000 deliveries.

The etiology of acute fatty liver of pregnancy is likely poor placental mitochondrial function. Many cases may be

due to a homozygous fetal deficiency of long-chain acyl coenzyme A dehydrogenase (LCHAD).

Clinical Findings

Clinical onset is gradual, with nausea and vomiting being the most common presenting symptoms. Varying degrees of flu-like symptoms are also typical. Eventually, symptoms progress to those of fulminant hepatic failure: jaundice, encephalopathy, disseminated intravascular coagulation, and death. On examination, the patient shows signs of hepatic failure.

Laboratory findings include marked elevation of alkaline phosphatase but only moderate elevations of ALT and AST. Hypocholesterolemia and hypofibrinogenemia are typical, and hypoglycemia can be extreme. Coagulopathy is also frequently seen with depressed procoagulant protein production. Kidney function should be assessed for hepatorenal syndrome. The WBC count is elevated, and the platelet count is depressed.

Differential Diagnosis

The differential diagnosis is that of fulminant hepatitis. Liver aminotransferases for fulminant hepatitis are higher (greater than 1000 U/mL) than those for acute fatty liver of pregnancy (usually 500–1000 U/mL). Preeclampsia may involve the liver but rarely causes jaundice; the elevations in liver biochemical tests in patients with preeclampsia rarely reach the levels seen in patients with acute fatty liver of pregnancy.

Treatment

Diagnosis of acute fatty liver of pregnancy mandates immediate delivery. Intensive supportive care with ICU-level observation is essential and typically includes administration of blood products and glucose and correction of acidemia. Vaginal delivery is preferred. Resolution of encephalopathy and laboratory derangements occurs over days with supportive care, and recovery is usually complete. Rare cases of liver transplantation have been reported.

Nelson DB et al. Acute fatty liver of pregnancy. Clin Obstet Gynecol. 2020;63:152. [PMID: 31725416]

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Intrahepatic cholestasis of pregnancy is characterized by incomplete clearance of bile acids in genetically susceptible women. The principal symptom is pruritus, which can be generalized but tends to have a predilection for the palms and soles. Presentation is typically in the third trimester, and women with multifetal pregnancies are at increased risk. The finding of an elevated serum bile acid level, ideally performed in the fasting state, confirms the diagnosis. Associated laboratory derangements include modest elevations in hepatic transaminase levels and mild hyperbilirubinemia. Although rare, the bilirubin level may be sufficiently elevated to result in clinical jaundice. The symptoms and laboratory abnormalities resolve quickly after delivery but can recur in subsequent pregnancies or with exposure to combination oral contraceptives.

Adverse fetal outcomes, particularly preterm birth, nonreassuring fetal status, meconium-stained amniotic fluid, and stillbirth, have consistently been reported in women with cholestasis of pregnancy. The risk for adverse perinatal outcomes appears to correlate with disease severity as measured by the degree of bile acid elevation, and women with fasting bile acids greater than 40 mcmol/L have been reported to be at greatest risk. Because of the risks associated with cholestasis of pregnancy, many clinicians recommend antenatal testing in the third trimester, and if cholestasis is present, elective early delivery to reduce the risk of stillbirth. The diagnosis of cholestasis of pregnancy is made when the level of bile salts is 10 mcmol/L or more (not necessarily fasting) with maternal symptoms. The Society for Maternal-Fetal Medicine (SMFM) 2021 recommends early delivery (36 weeks' gestation) when the patient's bile acid level is greater than 100 mcmol/L and other fetal tests are normal; in the symptomatic patient whose bile acid level is below 100 mcmol/L, the SMFM suggests delivery between 36 and 39 weeks' gestation. The ACOG endorses ursodeoxycholic acid as the first-line agent for the treatment of maternal symptoms of intrahepatic cholestasis of pregnancy. A 2019 randomized controlled trial did not find that ursodeoxycholic acid improved perinatal outcomes.

Lee RH et al. Society for Maternal-Fetal Medicine Consult Series No. 53: intrahepatic cholestasis of pregnancy: replaces Consult No. 13. Am J Obstet Gynecol. 2021;224:B2. [PMID: 33197417]

APPENDICITIS

Appendicitis occurs in about 1 of 1500 pregnancies. The diagnosis is more difficult to make clinically in pregnant women where the appendix is displaced cephalad from McBurney point. Furthermore, nausea, vomiting, and mild leukocytosis occur in normal pregnancy, so with or without these findings, any complaint of right-sided pain should raise suspicion. Imaging can help confirm the diagnosis if clinical findings are equivocal. Abdominal sonography is a reasonable initial imaging choice, but nonvisualization of the appendix is common in pregnancy. CT scanning is more sensitive than ultrasound, and with proper shielding, the radiation exposure to the fetus is minimized. MRI is also used to evaluate for appendicitis in pregnant women and is a reasonable alternative to CT scanning.

An operative approach to appendicitis, rather than a conservative nonoperative approach, is indicated for pregnant patients. Conservative management is associated with increases in maternal morbidity, including septic shock, peritonitis, and venous thromboembolism.

Unfortunately, the diagnosis of appendicitis is not made until the appendix has ruptured in at least 20% of obstetric patients. Peritonitis in these cases can lead to preterm labor or abortion. With early diagnosis and appendectomy, the prognosis is good for mother and baby.

Weinstein MS et al. Appendicitis and cholecystitis in pregnancy. Clin Obstet Gynecol. 2020;63:405. [PMID: 32187083]